Drug therapy for low cardiac output syndrome in paediatric patients with open heart surgery

Characterisation, Paediatric needs assessment and Optimisation

Winnie Vogt

Drug therapy for low cardiac output syndrome in paediatric patients with open heart surgery

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Ich versichere an Eides Statt, dass die Dissertation von mir selbständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität“ erstellt worden ist. Die Dissertation wurde in der vorgelegten oder in ähnlicher Form noch bei keiner anderen Institution eingereicht. Ich habe bisher keine erfolglosen Promotionsversuche unternommen.

Düsseldorf, den

(Winnie Vogt)

To Maia and Anartz

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Chapter 1

Introduction

Drug therapy in neonates, infants, children and adolescents with congenital heart disease is an essential component of medical care alongside surgical and catheter interventions. It aims at treating, palliating and preventing disease, disease progression and associated illnesses. Despite its clear necessity within the patient care cycle, drug therapy for paediatric patients with congenital heart disease has been characterised by a lack of sufficiently labelled medication [1, 2], which sets hurdles to healthcare professionals in providing safe, effective and high quality drug therapy. This is especially true for paediatric patients in need for postoperative cardiac support for low cardiac output syndrome (LCOS), which is a serious complication after cardiac surgery with cardiopulmonary bypass also referred to as open heart surgery.

Congenital heart disease is the most common type of birth defects [3] and assembles "a gross structural abnormality of the heart and intrathoracic great vessels that is actually or potentially of functional significance" [4]. It affects approximately 8 per 1000 live births [5]. Fortunately, the majority of paediatric patients do not require invasive intervention because they present with mild forms of congenital heart disease, such as small ventricle septum defects [6]. These lesions may be asymptomatic and can undergo early spontaneous resolution. However, patients with moderately severe forms of congenital heart disease, such as large ventricle defects or tetralogy of Fallot, require invasive cardiosurgery or catheter interventions often within the first year of life to ensure survival and minimise functional maladaptations of other organs over time. According to the national aggregate data for congenital heart disease in the United Kingdom [7] from 2010 to 2011, 6871 paediatric patients aged 0-16 years required invasive interventions, of which 51% were less than 1 year old. In fact, the percentage rose to 66% when the focus was on surgical interventions only, which were performed twice more often than catheter interventions. Open heart surgery was performed in two third of the cases, which renders it the mostly utilised invasive intervention for congenital heart disease in early life.

Open heart surgery is made possible by employing cardiopulmonary bypass, a technique that temporarily replaces the pump- and oxygenation function of the heart and lungs and enables a bloodless surgical field while operating a non-beating heart [8]. In simple terms, an arterial cannula is most often inserted into the aorta or femoral artery and a venous cannula into the right atrium and/or vena cava. Venous blood is drained from the patient into the bypass system, oxygenated and pumped back to the patient via the arterial cannula. To achieve a bloodless surgical field, aortic cross clamps are inserted, which necessitate myocardial protection to avoid myocardial ischemia. Despite this simplistic description of cardiopulmonary bypass, the immaturity of organ function, significant haemodilution, hypothermia and the need for circulatory arrest make paediatric patients especially vulnerable to open heart surgery [8]. Consequently, postoperative complications are common, of which low cardiac output syndrome is the single most determining factor for morbidity and mortality in paediatric patients [9].

LCOS develops in approximately 25% of paediatric patients following open heart surgery [10] and is characterised by a transient drop in cardiac output 6-18 hours after surgery [11]. Poor organ perfusion, tachycardia, oliguria or cardiac arrest with and without metabolic acidosis and widened arterial-mixed venous oxygen saturation have been used for diagnostic purposes [10] although a consensus-based definition of LCOS is still lacking. The causes of LCOS are multifactorial and have been implicated with the inflammatory response to cardiopulmonary bypass, myocardial ischemia due to prolonged cross-clamping, reperfusion injury and hypothermia as well as residual or undiagnosed structural lesions [12]. In all, they can lead to the detrimental effects of LCOS, namely multiorgan damage, if not timely recognised and managed. LCOS has been identified to be the main cause for acute renal failure following open heart surgery [13]; it also contributes to cerebral damage [14] and results in prolonged mechanical ventilation [15] and intensive care unit stay [10]. Consequently, healthcare professionals have turned their attention at reducing postoperative morbidity and mortality associated with LCOS by adopting appropriate means for its treatment and prevention, which also involves the use of drugs.

Drug therapy for paediatric LCOS, however, is a challenging endeavour for healthcare professionals. Despite a large amount of drugs available with inotropic, vasopressor and vasodilatory properties, only two drugs are currently licensed for LCOS treatment in paediatrics and none for LCOS prevention. The first drug, dobutamine, is licensed for inotropic support in paediatric patients after congenital heart surgery in two European countries [16] but significant gaps in the product label do not ease drug administration: A 15-fold range in dosing is provided although the Summary of Product Characteristics (SmPC) simultaneously highlights dobutamine's narrow therapeutic index in paediatrics [17]. The lack of efficacy data also complicates its use in neonates [18]. The second drug, milrinone, has been only recently approved in 2011/2012 for the treatment of LCOS in paediatric patients across Europe [19] but similarly to dobutamine, insufficient labelling hampers its safe and effective use [20]. Other drugs, such as levosimendan [21], dopamine and epinephrine [22], are also used for paediatric LCOS but off-label, which means their use is outside the product label of the marketed drug with regard to the therapeutic indication [23].

The importance of off-label drug prescribing, however, lies in the fact that the drugs have not been subjected to a rigorous approval process that ensures high standards of drug safety, quality and efficacy for a specific indication and age group. Reasons for the neglect of conducting clinical trials in paediatric patients include ethical and commercial aspects [24]. In paediatric patients with cardiovascular medication, further barriers are due to the relative rarity of disease, the heterogeneous presentation of the disease, insufficient research infrastructure and difficulties in identifying valid clinical end points [25]. In summary, more than 50% of the cardiovascular medication in paediatric patients hospitalised with congenital and acquired heart disease is used off-label [1]. In addition, the more specialised the required procedures and the younger the affected patients are, the higher is the

off-label drug use. For example, 92-100% of drugs for cardiac-surgical and transplant paediatric patients are used off-label with the inherent risk of increased patient harm and/or lack of efficacy [1].

Adverse drug reactions associated with paediatric off-label drug use are serious and reflect the limited evidence available on the appropriate use of drugs [26]. Therefore, it is not surprising that younger patients and those requiring more specialised treatment experience more adverse drug reactions than other paediatric patients. This has been demonstrated in the study by Turner et al. [27] investigating the off-label and unlicensed use of drugs in paediatric patients admitted to different wards. Those paediatric patients admitted to a paediatric cardiac intensive care unit were three times more likely to be prescribed off-label and unlicensed drugs and five times more likely to experience adverse drug reactions than paediatric patients admitted to a medical ward. The study by Maltz et al. [28] also showed that paediatric patients admitted to the cardiac intensive care unit and prescribed a high load of off-label drugs, stayed three times longer in hospitals and twice as long on a ventilator than patients prescribed less off-label drugs on the same ward. The problem is omnipresent and guidelines have been published in an effort to rationalise off-label prescribing [29, 30]. Nonetheless, they do not address the core of the problem, which is the limited evidence available on the appropriate use of drugs in paediatric patients.

The European Regulation on medicines for paediatric use [16], which came into force in January 2007, was launched to overcome this barrier and improve the health of children in Europe by ensuring that medicines are subject to high quality research and appropriately authorised for use in paediatrics. A system of requirements and incentives was established for the pharmaceutical industry to trigger research and development of new medicines and off-patent products for use in the paediatric population. In addition, the Paediatric Committee at the European Medicines Agency (EMA) has identified the paediatric needs in different therapeutic areas, including cardiovascular products [31], where research and development is highly required. The decision on which drugs to include has been based on the work of the former Paediatric Working Party in consultation with experts [32] and the "Report on the survey of all paediatric uses of medicinal products in Europe" from 2010 [33]. However, the actual needs of paediatric patients with LCOS after open heart surgery cannot be fully represented because the aforementioned survey report did not cover 48% of the European paediatric population. Sadly, Germany as a country with many specialised centres for paediatric patients with congenital heart disease did not provide any data. Of those countries that submitted information, data was very heterogeneous and included a mix of inpatient, outpatient and primary care data. Therefore, no data is currently available that describes hospital practice with regard to drug use for paediatric LCOS to enable an objective decision-making on potential paediatric needs.

Thus, there is an urge for a quantitative description of drug use for LCOS in paediatric patients with open heart surgery to base any future decision on drug research and development as well as associated funding on objective rather than subjective criteria towards encompassing actual paediatric needs.

Following the identification of paediatric needs in this field, research and development must ultimately address current problems associated with drug use in paediatrics, and the related causes of harm can be manifold [24]. A major aspect, however, can be attributed to the incomplete knowledge and/or understanding about the patho- and physiological differences between adults and paediatrics as well as pharmacokinetic and pharmacodynamic drug characteristics in neonates, infants, children and adolescents [34, 35]. Due to the limited evidence available, doses for paediatric patients are often delineated from adults using linear relationships between dose and bodyweight, body surface area or other demographic covariates although it is not always known how these factors affect drug exposure in young patients [36]. Empirical scaling approaches and the incomplete understanding of the interferences led to the development of the fatal gray-baby-syndrome due to supratherapeutic plasma levels of chloramphenicol because the adult bodyweight-normalised dose was administered to neonates with still immature renal function and glucuronidation [37]. In contrast, linear scaling based on bodyweight can also result in subtherapeutic level and, therefore, lack of efficacy as shown for carbamazepine with higher Cytochrome P450 3A4 (CYP3A4) mediated clearances in children than adults [38]. Albeit not as well studied, developmental changes in the pharmacodynamics may equally provoke an age-dependent response to drug therapy in neonates, infants, children and adolescents, such as the impaired inotropic response to dopamine in preterms and neonates due the immaturity of the myocardium [39]. The matter is further complicated in critically ill paediatric patients with open heart surgery, which necessitates not only the considerations of organ development and maturation on the pharmacokinetics of drugs but also pre- and postoperative disease characteristics as well as the effects of cardiopulmonary bypass on haematocrit, haemodilution and protein abundance [40].

Clearly, empirical scaling approaches from adults to paediatrics cannot encompass the age-related growth and maturation processes across all paediatric age groups, which affect absorption, distribution, metabolism and excretion of drugs. Tissue composition changes with age, also organ weights and blood flow rates as well as enzyme activity and functionality of elimination processes [41]. Disease, comorbidities and external appliances, such as cardiopulmonary bypass, also alter drug exposure and/or response [40, 42, 43]. The EMA has addressed this field and recommended the use of modelling and simulation as supportive tools. The tools shall fill the gaps of drug-response knowledge in paediatrics without subjecting paediatric patients to unnecessary clinical trials and by making best use of existing pharmacokinetic and pharmacodynamic data from adults, paediatrics and experimental studies [44].

A system-biology based approach, such as physiology-based pharmacokinetic (PBPK) modelling and simulation may be best suited to address the gap of knowledge in paediatric drug use. In a whole-body PBPK model, the organism is subdivided into several compartments representing the relevant organs and tissues, which are interconnected by arterial and venous blood pools; mass-balance equations describe the inter-tissue mass transport and the incorporation of physicochemical drug properties allows the prediction of drug exposure in blood, plasma and different organs [45]. This way, PBPK modelling provides mechanistic insights into the interplay of drugs, organs, tissue composition and blood flow but also also the incorporation of variability associated with aging, disease and concurrent therapies. Its usefulness has been demonstrated in adult patients with liver [46] and renal disease [47] and non-cardiac surgery [48]. The incorporation of the knowledge on organ growth and maturation has also successfully enabled the prediction of drug exposure in paediatric patients [41]. Furthermore, PBPK modelling allows the consideration and utilisation of pharmacokinetic- and pharmacodynamic-related knowledge from other patient population and healthy volunteers, as well as the extrapolation and the inclusion of experimental data as requested by the EMA to make medicines child-size [44].

Bridging drug pharmacokinetics from adults to paediatrics becomes especially valuable for *a-priori* prediction of drug exposure in paediatrics, which is required to accompany the European [16] and US American [49] marketing authorisation applications for new drugs with potential benefit in paediatric patients. However, if indication, mechanism, course and outcome of disease differ between adults and paediatrics, as it is the case for paediatric LCOS, the concept of bridging provides only limited value [50]. In this case, disease models can help to reveal similarities and differences between adult and paediatric drug exposure, for which the potential of PBPK drug-disease modelling has been equally recognised by European [51] and US regulatory [52] authorities towards improving paediatric patients' access to safe and effective drug therapy.

The lack of PBPK drug-disease models for paediatric LCOS after open heart surgery, however, hampers the evaluation and optimisation of current drug therapy that needs to be endeavoured given the limited evidence on drug use and the acute life-threatening clinical scenario of LCOS.

AIM & OBJECTIVES

Drug therapy for paediatric LCOS after open heart surgery is characterised by insufficient evidence to ensure safe and effective drug use, which ultimately puts paediatric patients at risk of experiencing adverse drug reactions and/or inefficient therapy. In consequence, healthcare professionals and regulatory authorities are requesting more information on the use of drugs in this field to identify paediatric needs where research and development is highly required. Moreover, there is an urge for an effective method to better understand and describe the pharmacokinetics of drugs in paediatric patients that should take into account the influence of disease by maximising the learning from existing clinical and experimental data and minimising the burden of clinical trials in paediatrics. The aim of this thesis is, therefore, to contribute to a better use of medicine for neonates, infants, children and adolescents with open heart surgery by unrevealing the prescribing pattern for LCOS, identifying paediatric needs and developing a novel model-based approach to embrace the developmental changes across paediatric ages and the various effects of disease and open heart surgery on drug exposure. The integrated research approach should directly translate into clinical practice applications by providing age-appropriate optimised dosing strategies that clinicians can opt for the drug with the highest potential of contributing to safer and more effective drug therapy for LCOS. The objectives of this thesis can be delineated as follows:

1. To describe the European hospital practice pattern for LCOS treatment and prevention in paediatric patients with open heart surgery for repair or palliation of congenital heart disease.
2. To identify the drug with the highest potential of contributing to safer and more effective LCOS treatment and prevention.
3. To develop and evaluate a whole-body PBPK drug-disease model for the identified drug in paediatric patients with (treatment) and without (prevention) LCOS after open heart surgery.
4. To evaluate and optimise current dosing regimens of the identified drug for paediatric LCOS using the PBPK drug-disease model.
5. To provide insight into the capabilities of system-biology modelling and simulation as an exploratory tool for improving drug dosing in paediatric patients.

OUTLINE

The thesis consists of five chapters, of which the current *Chapter 1* provides a brief introduction to the conflicting issues related to drug prescribing for paediatric patients with LCOS after open heart surgery. It addresses off-label drug use and associated harm, initiatives by regulatory authorities to improve access to safe, effective and labelled paediatric drugs as well as the role of modelling and simulation to support these endeavours with a focus on paediatric LCOS.

Chapter 2 describes the methodology of the web-based European-wide survey on the pharmacological management of LCOS in paediatric patients after open heart surgery, short EuLoCOS-Paed, and presents the first two parts of the survey results: the current hospital practice pattern for paediatric LCOS treatment and the availability and use of prescribing resources in this field.

In *Chapter 3*, the last part of the results from EuLoCOS-Paed are presented revealing the prescribing pattern for paediatric LCOS prevention (*Chapter 3.1*), and its stratification into individual drug use (*Chapter 3.2*). Like this, the results complement the findings presented in *Chapter 2* and provide extensive insight into the prescribing pattern of European hospitals. This, in turn, allows the identification of paediatric needs.

Based on the paediatric needs assessment from EuLoCOS-Paed, the drug with the highest potential to contribute to safer and more effective use of medicine for paediatric LCOS is identified based on the frequency reports in the survey and reported variability with regard to the mode of drug administration. The drug candidate is embraced in a novel PBPK drug-disease model to characterise drug exposure in paediatric patients with (treatment) and without (prevention) LCOS.

Chapter 4 describes the development and evaluation of the PBPK drug-disease model as well as the evaluation and optimisation of current dosing regimens of the identified drug candidate in paediatric LCOS. It also discusses the capabilities of PBPK drug-disease modelling and simulation and its potential as an exploratory tool for improving drug dosing in paediatric patients.

Finally, the thesis concludes in *Chapter 5* with a summary of the main findings, which are put into a broader perspective for discussion. The chapter also presents the lessons learned from EuLoCOS-Paed (*Chapter 2* and *Chapter 3*) and PBPK drug-disease modelling and simulation (*Chapter 4*) as well as their implications towards safer and more effective drug therapy for paediatric patients with LCOS.

REFERENCES

1 Pasquali SK, Hall M, Slonim AD, *et al.* Off-label use of cardiovascular medications in children hospitalized with congenital and acquired heart disease. *Circ Cardiovasc Qual Outcomes* 2008;1(2):74–83.

2 Hsien L, Breddemann A, Frobel AK, *et al.* Off-label drug use among hospitalised children: identifying areas with the highest need for research. *Pharm World Sci* 2008;30(5):497-502.

3 Centers for Disease Control and Prevention. Congenital heart defects: Data & statistics 2011. http://www.cdc.gov/ncbddd/heartdefects/data.html. Accessed 5 Mar 2013.

4 Mitchell SC, Korones SB, Berendes HW. Congenital heart disease in 56,109 births. Incidence and natural history. *Circulation* 1971;43(3):323–332.

5 Moons P, Sluysmans T, de Wolf D, *et al.* Congenital heart disease in 111 225 births in Belgium: birth prevalence, treatment and survival in the 21st century. *Acta Paediatr* 2009;98(3):472–477.

6 Hoffman JIE, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol* 2002;39(12):1890–1900.

7 National Institute for Cardiovascular Outcomes Research. Congenital heart disease website - National statistics. https://nicor4.nicor.org.uk/CHD/an_paeds.nsf/WMortality?Openview. Accessed 9 Jan 2013.

8 Jaggers J, Ungerleider RM. Cardiopulmonary bypass in infants and children. In: Nichols DG, Ungerleider RM, Spevak PJ, et al., Eds. Critical heart disease in infants and children, 2nd Edn. Philadelphia, PA: Mosby Elsevier 2006:507–528.

9 Ma M, Gauvreau K, Allan CK, *et al.* Causes of death after congenital heart surgery. *Ann Thorac Surg* 2007;83(4):1438–1445.

10 Hoffman TM, Wernovsky, G, Atz, AM, *et al.* Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation* 2003;107(7):996–1002.

11 Wernovsky G, Wypij D, Jonas RA, *et al.* Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. *Circulation* 1995;92(8):2226–2235.

12 Wessel DL. Managing low cardiac output syndrome after congenital heart surgery. *Crit Care Med* 2001;29(10 Suppl):S220-S230.

13 Chiravuri SD, Riegger LQ, Christensen R, *et al.* Factors associated with acute kidney injury or failure in children undergoing cardiopulmonary bypass: a case-controlled study. *Paediatr Anaesth* 2011;21(8):880–886.

14 Ballweg JA, Wernovsky G, Gaynor JW. Neurodevelopmental outcomes following congenital heart surgery. *Pediatr Cardiol* 2007;28(2):126–133.

15 Shi S, Zhao Z, Liu X, *et al.* Perioperative risk factors for prolonged mechanical ventilation following cardiac surgery in neonates and young infants. *Chest* 2008;134(4):768–774.

16 European Parliament and the Council. Regulation (EC) No 1901/2006 of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. *Official Journal of the European Union* 2006;L378:1–19.

17 Fresenius Kabi Deutschland. Summary of Product Characteristics for Dobutamin Liquid Fresenius 250 mg/50 ml Infusionslösung (INN: Dobutamine) 2008. http://www.fachinfo.de. Accessed 1 Jul 2013.

18 European Medicines Agency. Revised priority list for studies into off-patent paediatric medicinal products for the Fifth Call 2011 of the 7th Framework Programme of the European Commission, Rev. 2010 (Doc. Ref.: EMA/253396/2010).

19 European Medicines Agency. Milrinone: Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended 2011.

20 Sanofi Aventis. Summary of Product Characteristics for Primacor 1mg/ml Solution for Injection (INN: Milrinone) 2011. http://www.medicines.org.uk/EMC/medicine/6984/SPC/Primacor+1mg+ml+Solution+for+Injection/. Accessed 9 Jul 2012.

21 Suominen PK. Single-center experience with levosimendan in children undergoing cardiac surgery and in children with decompensated heart failure. *BMC Anesthesiol* 2011;11:18

22 Gaies MG, Gurney JG, Yen AH, *et al.* Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med* 2010;11(2):234–238.

23 Neubert A, Wong ICK, Bonifazi A, *et al.* Defining off-label and unlicensed use of medicines for children: results of a Delphi survey. *Pharmacol Res* 2008;58(5-6):316–322.

24 Kimland E, Odlind V. Off-label drug use in pediatric patients. *Clin Pharmacol Ther* 2012;91(5):796–801.

25 Lipshultz SE, Wilkinson JD, Messiah SE, *et al.* Clinical research directions in pediatric cardiology. *Curr Opin Pediatr* 2009;21(5):585–593.

26 European Medicines Agency. Evidence of harm from off-label or unlicensed medicines in children (EMEA/126327/2004) 2004. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004021.pdf. Accessed 11 Mar 2013.

27 Turner S, Nunn AJ, Fielding K, *et al.* Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatr* 1999;88(9):965–968.

28 Maltz LA, Klugman D, Wessel DL. Off-label drug use in a single center pediatric cardiac intensive care unit. Presented at the American Academy of Pediatrics (AAP) National Conference and Exhibition in Washington, DC: October 17-20, 2009.

https://aap.confex.com/aap/2009/webprogram/Paper6427.html. Accessed 10 May 2011.

29 Gazarian M, Kelly M, McPhee JR, *et al.* Off-label use of medicines: consensus recommendations for evaluating appropriateness. *Med J Aust* 2006;185(10):544–548.

30 Verhagen CC, Niezink AG, Engels YY, *et al.* Off-label use of drugs in pain medicine and palliative care: an algorithm for the assessment of its safe and legal prescription. *Pain Pract* 2008;8(3):157–163.

31 European Medicines Agency. Inventory of paediatric medicines: Cardiovascular therapeutic area (EMA/550070/2012) 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/08/WC500131636.pdf. Accessed 11 Mar 2013.

32 European Medicines Agency. EMEA/PEG Procedure for identifying paediatric needs (EMEA/175192/2004/rev2) 2005. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004036.pdf. Accessed 11 Mar 2013.

33 European Medicines Agency. Report on the survey of all paediatric uses of medicinal products in Europe (EMA/794083/2009) 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101006.pdf. Accessed 11 Mar 2013.

34 Kearns GL, Abdel-Rahman SM, Alander SW, *et al.* Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003;349(12):1157–1167.

35 Macleod S. Therapeutic drug monitoring in pediatrics: how do children differ? *Ther Drug Monit* 2010;32(3):253–256.

36 Cella M, Knibbe C, Danhof M, *et al.* What is the right dose for children? *Br J Clin Pharmacol* 2010;70(4):597–603.

37 Weiss CF, Glazko AJ, Weston JK. Chloramphenicol in the newborn infant. A physiologic explanation of its toxicity when given in excessive doses. *N Engl J Med* 1960;262:787–794.

38 Pynnönen S, Sillanpää M, Frey H, *et al.* Carbamazepine and its 10,11-epoxide in children and adults with epilepsy. *Eur J Clin Pharmacol* 1977;11(2):129–133.

39 Cox DJ, Groves AM. Inotropes in preterm infants--evidence for and against. *Acta Paediatr Suppl* 2012;101(464):17–23.

40 van Saet A, de Wildt SN, Knibbe CAJ, *et al.* The Effect of Adult and Pediatric Cardiopulmonary Bypass on Pharmacokinetic and Pharmacodynamic Parameters. *Curr Clin Pharmacol* 2012 Dec 10. [Epub ahead of print].

41 Edginton AN, Schmitt W, Willmann S. Development and evaluation of a generic physiologically based pharmacokinetic model for children. *Clin Pharmacokinet* 2006;45(10):1013–1034.

42 Rodighiero V. Effects of cardiovascular disease on pharmacokinetics. *Cardiovasc Drugs Ther* 1989;3(5):711–730.

43 Krishnaswamy K. Drug metabolism and pharmacokinetics in malnourished children. *Clin Pharmacokinet* 1989;17(Suppl 1):68–88.

44 European Medicines Agency. Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (Doc. Ref. EMEA/CHMP/EWP/147013/2004). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003066.pdf. Accessed 5 Feb 2013.

45 Rowland M, Peck C, Tucker G. Physiologically-based pharmacokinetics in drug development and regulatory science. *Annu Rev Pharmacol Toxicol* 2011;51:45–73.

46 Edginton AN, Willmann S. Physiology-based simulations of a pathological condition: prediction of pharmacokinetics in patients with liver cirrhosis. *Clin Pharmacokinet* 2008;47(11):743–752.

47 Zhao P, de Vieira MLT, Grillo JA*, et al.* Evaluation of exposure change of nonrenally eliminated drugs in patients with chronic kidney disease using physiologically based pharmacokinetic modeling and simulation. *J Clin Pharmacol* 2012;52(1 Suppl):91S-108S.

48 Björkman S, Wada DR, Berling BM*, et al.* Prediction of the disposition of midazolam in surgical patients by a physiologically based pharmacokinetic model. *J Pharm Sci* 2001;90(9):1226–1241.

49 IOM (Institute of Medicine). Safe and effective medicines for children: Pediatric studies conducted under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. Washington, DC: The National Academies Press 2012.

50 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for industry: exposure-response relationship - study design, data analysis, and regulatory applications. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf. Accessed 16 Mar 2013.

51 Jönsson S, Henningsson A. Regulatory vision of paediatric applications. http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500009845.pdf. Accessed 16 Mar 2013.

52 Gobburu J. How to double success rate of pediatric trials? Conference proceedings of ASCPT. Atlanta, GA: 2010. http://www.slideshare.net/JogaGobburu/how-to-double-success-rate-of-pediatric-trials. Accessed 16 Mar 2013.

Chapter 2

TREATING PAEDIATRIC LOW CARDIAC OUTPUT SYNDROME

TREATMENT FOR PAEDIATRIC LOW CARDIAC OUTPUT SYNDROME: RESULTS FROM THE EUROPEAN EULOCOS-PAED SURVEY

WINNIE VOGT
STEPHANIE LÄER

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Original article

Treatment for paediatric low cardiac output syndrome: results from the European EuLoCOS-Paed survey

Winnie Vogt, Stephanie Läer

► Online supplementary figure 1 and online supplementary table 1 are available online only. To view these files please visit the journal website (http://adc.bmj.com/content/96/12.toc)

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ABSTRACT

Objective To characterise current hospital practice and use of prescribing resources related to drug treatment for low cardiac output syndrome (LCOS) in children with open heart surgery (OHS) in Europe.

Design A web-based questionnaire survey (EuLoCOS-Paed) conducted between January and August 2009.

Setting European hospitals performing OHS in children.

Results 90 out of 125 hospitals (72%) from 31 European countries responded to the questionnaire. The initial treatment and two add-on steps reported were analysed for: (i) LCOS with elevated systemic vascular resistance (SVR), where milrinone (34% of reports), epinephrine (24%) and epinephrine/levosimendan (22%) were favoured; (ii) LCOS with low SVR, where dopamine (20%), epinephrine (29%) and norepinephrine (24%) were dominant; and (iii) LCOS with elevated pulmonary vascular resistance, where milrinone (17%), inhaled nitric oxide (20%) and prostacyclin derivatives (22%) were preferred. Overall, milrinone, epinephrine, dopamine and dobutamine were used in over 50% of the reported drug regimens for treating LCOS. The availability of drug and dosing information for prescribing was stated to be insufficient by 40% of participants, while 88% would appreciate clinical practice guidelines.

Conclusion Drug treatment for LCOS in children with OHS across Europe is highly variable, possibly partly reflecting the lack of evidence and prescribing standards on the use of medicines. Milrinone, epinephrine, dopamine and dobutamine are mostly used, and should be prioritised for future research on LCOS treatment. Such research should be aimed at increasing the level of evidence for clinical practice guidelines to improve the standard of care.

What is already known on this topic

- Low cardiac output syndrome (LCOS) is common following open heart surgery and is associated with increased morbidity and mortality.
- Cardiovascular drugs in children are commonly used on the basis of adult trials.
- Specific European guidelines on the safe and effective use of drugs for the treatment of LCOS in children are lacking.

What this study adds

- LCOS treatment in children varies widely across Europe with up to 23 drugs and 39 drug regimens used.
- Many survey participants would value effective drug and dosing information for paediatric prescribing and use.
- Milrinone, dopamine, dobutamine and epinephrine are used by approximately 50% of participants and should be evaluated for safety and efficacy in children.

INTRODUCTION

Low cardiac output syndrome (LCOS) remains a serious complication affecting approximately 25% of children with open heart surgery (OHS) in the postoperative period.[1] It is associated with longer mechanical ventilation[2] and prolonged hospital stay[1] and has been identified as the main cause of death in children after OHS.[3]

Since LCOS is a major contributing factor to morbidity and mortality, vasoactive drugs are routinely used to treat it.[4] However, selecting and prescribing drugs for children with LCOS is a challenging task for healthcare professionals. There are no specific guidelines on the postoperative management of children with OHS. Septic shock guidelines, which address LCOS in children, are limited in their recommendations by the grade C evidence available.[5 6] Furthermore, dosing guidance is not available for over half of the available cardiac drugs[7] and only dobutamine is licensed for inotropic support in children following OHS in Spain and Germany.[8] Therefore, off-label drug use is common practice[9] and may be associated with increased risk of ineffective drug treatment and adverse drug reactions in children.[10 11] Consequently, although there is a need for intensified research in this area, the lack of quantitative data on drug use makes decisions on which drugs to focus in future clinical research difficult, which point has been emphasised by the Cardiology Group on Postoperative Cardiac Dysfunction.[4]

The aim of this study was to characterise current hospital practice and use of prescribing resources with regard to drug treatment for LCOS in children with OHS across Europe. The results complement previously published studies on LCOS prevention[12 13] and may guide decision-making in prioritising those drugs most requiring research in this setting and in promoting safe and effective drug treatment in children with OHS.

Drug therapy

METHODS

Survey instrument development

Development of the EuLoCOS-Paed questionnaire was guided by previous surveys on vasoactive drug use in adult patients[14–16] and guidelines on cardiac and circulatory failure in adult and paediatric care.[5 6 17 18] Standard survey methods for mail and web-based surveys were also adopted to increase the overall response rate.[19 20]

As suggested by Presser,[21] an expert panel consisting of nine European experts in the fields of paediatric cardiology, anaesthesiology, intensive care, cardiac surgery and general medicine, and two experts in survey design reviewed and pilot-tested the questionnaire in two stages.

The questionnaire (online supplementary figure 1) consisted of 15 questions divided into four sections: sources of information for prescribing, drug therapy for LCOS, preventive drug therapy for LCOS (data not shown), and participant characteristics and comments. LCOS treatment was classified into subtypes of LCOS with elevated and low systemic vascular resistance (SVR), and elevated pulmonary vascular resistance (PVR), and information on treatment algorithms was requested. Participants were asked which drug regimens (monotherapy and/or combination therapy) they used for initial treatment of LCOS in fluid-optimised patients, and which drugs they added in the next two steps if initial treatment was insufficient.

The questionnaire was designed to be completed in 5 min and aimed to obtain a response rate of at least 60–70% for external validity.[22] For this reason, time-consuming questions on outcome data, average volume and the complexity of OHS performed in hospitals were omitted. The questionnaire was integrated into a web-based survey platform (EFS Survey V.6.0; Globalpark, Huerth, Germany).

Table 1 Treatment algorithms for LCOS identified from the drug regimens reported for initial treatment and first and second add-on treatment for each LCOS subtype

	Generic drug name analysis				Therapeutic drug class analysis			
Step	**Reports***	**Drug regimen**	**N (%)**	**95% CI**	**Reports***	**Drug regimen**	**N (%)**	**95% CI**
LCOS with elevated SVR								
Initial treatment	32/90	Mil	31 (34)	25 to 45†	22/90	Inodil	34 (38)	28 to 48†
		Dob+Mil	7 (8)	4 to 15		Inodil+Inotrop	10 (11)	6 to 19
		Dop+Mil	7 (8)	4 to 15		Inodil+Inovas	7 (8)	4 to 15
						Vasodil	7 (8)	4 to 15
First add-on	27/87	Epi	21 (24)	16 to 34	14/87	Inotrop	26 (30)	21 to 40
		Mil	10 (11)	6 to 20		Vasodil	17 (20)	13 to 29
		SNP	8 (9)	5 to 17		Inodil	16 (18)	12 to 28
Second add-on	14/41	Epi	9 (22)	12 to 37	10/41	Inotrop	14 (34)	22 to 49
		Lev	9 (22)	12 to 37		Inodil	13 (32)	20 to 47
		Dob	5 (12)	5 to 26		Vasodil	5 (12)	5 to 26
LCOS with low SVR								
Initial treatment	21/89	Dop	18 (20)	13 to 30	15/89	Inovas	29 (33)	24 to 43
		Epi	15 (17)	10 to 26		Inotrop	19 (21)	14 to 31
		Nor	10 (11)	6 to 19		Inotrop+Inovas	14 (16)	10 to 25
First add-on	20/73	Epi	21 (29)	20 to 40	13/73	Inotrop	23 (32)	22 to 43
		Nor	18 (25)	16 to 36		Inovas	22 (30)	21 to 41
		Mil	6 (8)	4 to 17		Inodil	8 (11)	6 to 20
Second add-on	10/29	Nor	7 (24)	12 to 42	6/29	Inovas	7 (24)	12 to 42
		Epi	6 (21)	10 to 38		Vasopr	7 (24)	12 to 42
		Mil	4 (14)	6 to 31		Inotrop	6 (21)	10 to 38
		Vas	4 (14)	6 to 31		Inodil	6 (21)	10 to 38
LCOS with elevated PVR								
Initial treatment	39/87	Mil	15 (17)	11 to 27	20/87	Inodil	18 (21)	14 to 30
		iNO+Mil	11 (13)	7 to 21		Vasodil	12 (14)	8 to 23
		iNO	9 (10)	6 to 19		Vasodil+Inodil	12 (14)	8 to 23
First add-on	33/75	iNO	15 (20)	13 to 30	14/75	Vasodil	32 (43)	32 to 54†
		Epi	8 (11)	6 to 20		Inodil	11 (15)	8 to 24
		Sil	8 (11)	6 to 20		Inotrop	10 (13)	7 to 23
Second add-on	14/37	PGI	8 (22)	11 to 37	7/37	Vasodil	23 (62)	46 to 76†
		iNO	5 (14)	6 to 28		Inotrop	4 (11)	4 to 25
		Sil	5 (14)	6 to 28		Inodil	4 (11)	4 to 25

Participants were asked which drug regimens (monotherapy and/or combination therapy) they use for initial treatment for each LCOS subtype in fluid-optimised patients, and which drugs they add in the next two steps if initial treatment is insufficient. The table lists the three most reported drug regimens per treatment step and LCOS subtype.

*Reports refer to the number of different drug regimen reports (generic drug name and therapeutic drug class) per total number of drug regimen reports for the treatment step.

†Statistically significant difference between the 95% CI of the reports for the first and second ranked drug regimen within a LCOS subtype.

Dob, dobutamine; Dop, dopamine; Epi, epinephrine; iNO, inhaled nitric oxide; Inodil, inodilator; Inotrop, inotrope; Inovas, inovasopressor; LCOS, low cardiac output syndrome; Lev, levosimendan; Mil, milrinone; Nor, norepinephrine; PGI, prostacyclin derivatives (ie, answers given as prostacyclin, iloprost and epoprostenol); PVR, pulmonary vascular resistance; Sil, sildenafil; SNP, nitroprusside; SVR, systemic vascular resistance; Vas, vasopressin; Vasopr, vasopressor; Vasodil, vasodilator.

Table 2 Therapeutic drug classes for drugs used to treat LCOS subtypes within DU90% and total drug use

	LCOS with elevated SVR		LCOS with low SVR		LCOS with elevated PVR	
Therapeutic drug class	**N (%)**	**95% CI**	**N (%)**	**95% CI**	**N (%)**	**95% CI**
Inodilators	107 (35)*	29 to 40	29 (11)*	8 to 16	79 (26)*	22 to 32
Inotropes	88 (28)*	24 to 34	89 (34)*	29 to 40	48 (16)*	12 to 21
Inovasopressors	27 (9)*	6 to 12	118 (45)*	39 to 51	22 (7)	5 to 11
Vasodilators	77 (25)*	20 to 30	2 (1)	0 to 3	147 (49)*	43 to 55†
Analgesics and anaesthetics	5 (2)	1 to 4	–‡	0 to 1	4 (1)	1 to 3
Agents acting on the renin-angiotensin system	4 (1)	1 to 3	–	0 to 1	–	0 to 1
Muscle relaxants	1 (0)	0 to 2	–	0 to 1	–	0 to 1
Vasopressors	1 (0)	0 to 2	19 (7)	5 to 11	–	0 to 1
Corticosteroids	–	0 to 1	3 (1)	0 to 3	–	0 to 1

All individual drug reports grouped with respect to their therapeutic drug class were combined for each single LCOS subtype and ranked in descending order according to their frequency of reporting.[26] DU90% refers to the therapeutic drug classes accounting for 90% of total use.
*Therapeutic drug class accounting for 90% of the total use (DU90%) per LCOS subtype.
†Statistically significant difference between the 95% CI of the reports for the first and second ranked therapeutic drug class within a LCOS subtype.
‡Not reported.
DU, drug utilisation; LCOS, low cardiac output syndrome; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Survey participants

European hospitals that conduct OHS in children were identified from the European Association for Cardio-Thoracic Surgery Congenital Database, the Cardiothoracic Surgery Network member database and the hospital network list from the Association for European Paediatric Cardiology. The contact details of the clinicians caring for children with OHS were obtained from the web pages of national and European medical associations and hospitals, from European Congenital Heart Disease Organisation members and from personal contacts.

Survey administration

Participants received a personalised email informing them about the survey and inviting them to take part. The web link to the questionnaire and the password to enter it were included in the email. A reminder email was sent to non-responders 2 and 4 weeks after the initial email. Data were collected between January and August 2009.

Data grouping

In order to allow therapeutic drug class analysis and ensure drug use was comparable across countries, the drugs reported were grouped according to their therapeutic action. Cardiovascular drugs were classified according to Carcillo.[23] Since ACE inhibitors, corticosteroids, analgesics and anaesthetics, and muscle relaxants are not included in this classification, they were grouped separately according to the second level, that is, the therapeutic subgroup, of the Anatomical Therapeutic Chemical classification system.[24] Data grouping is shown in online supplementary table 1.

Data analysis

Individual drugs and drug regimens were analysed according to the number of times they were reported based on the generic drug name and the respective therapeutic drug class. The analysis was carried out for each treatment step separately. The results were expressed as percentages and displayed with their 95% CI, calculated using the Wilson method for single samples.[25] Missing data were excluded from the frequency counts.

Drug utilisation (DU) was analysed using the DU90% method as suggested by the WHO,[26] whereby all drugs reported for each LCOS subtype and their respective therapeutic drug class were combined and ranked in descending order according to their frequency of reporting. DU90% refers to those drugs accounting for 90% of total drug use focusing on the bulk of drugs prescribed; it can be adopted to provide comparative data on drug prescribing.

Since optimised fluid management was a prerequisite, drug entries mentioning diuretics and fluid volume were excluded from data analysis. Entries giving dose increases were also excluded because the focus was on drugs and not dosing. Oxygen, although a medical gas, was excluded because it was thought that the majority of participants did not consider oxygen a drug but rather part of other support measures and, therefore, did not report it.

Data analysis was performed with Microsoft Office Excel 2007 and CIA V.2.1.2[25] for the CI analysis.

Ethics approval

No ethics approval was required and the study complied with the Declaration of Helsinki.[27]

RESULTS

Survey participants

Responses were obtained from 90 of 125 eligible hospitals from 31 European countries, yielding a response rate of 72%. The main areas of specialisation of participants were paediatric cardiothoracic surgery (28%), anaesthesiology (26%), intensive care (22%) and cardiology (21%). Overall, 94% of participants had at least 5 years' experience in caring for children with OHS.

LCOS treatment algorithms

Milrinone monotherapy was the preferred drug regimen for the initial treatment of LCOS with elevated SVR (table 1), being reported significantly more often than a combination of milrinone with dobutamine or dopamine, which ranked second (34% vs 8%, 95% CI 25% to 45% vs 4% to 15%). Epinephrine was the preferred first add-on drug if initial treatment was insufficient (24%), and levosimendan or epinephrine was typically added in the next step (22% each).

In contrast, treatment of LCOS with low SVR was most often initiated with dopamine monotherapy (20%). Epinephrine was the most cited first add-on drug (29%), and norepinephrine was the preferred second add-on drug (24%).

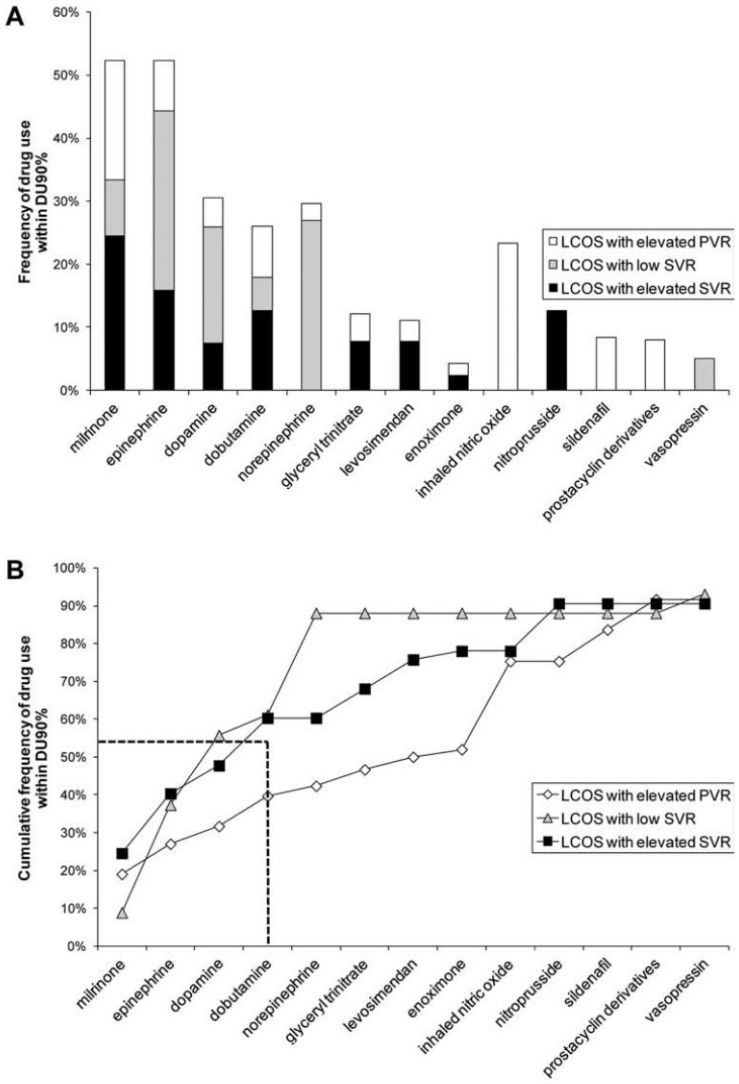

Figure 1 Frequency (A) and cumulative frequency (B) of drug use for low cardiac output syndrome (LCOS) subtypes within DU90%. DU90% refers to those drugs accounting for 90% of the total drug use, for which all drugs reported for each LCOS subtype were combined and ranked in descending order according to their frequency of reporting.[26] For LCOS with elevated systemic vascular resistance (SVR), eight out of 23 different drugs accounted for DU90%, for LCOS with low SVR, six out of 16 drugs accounted for DU90%, and for LCOS with elevated pulmonary vascular resistance (PVR), 11 out of 22 drugs accounted for DU90%. Milrinone, epinephrine, dopamine and dobutamine were in all DU90% segments; their combined use accounted for 54% of total drug use for all LCOS subtypes, which is represented by the dotted line in figure 1B (60% for LCOS with elevated SVR, 61% for LCOS with low SVR and 40% for LCOS with elevated PVR). Prostacyclin derivatives included reports with prostacyclin, iloprost and epoprostenol. DU, drug utilisation.

Milrinone monotherapy was the drug regimen of choice for the initial treatment of LCOS with elevated PVR (17%). The first and second add-on drugs most often reported were inhaled nitric oxide (20%) and prostacyclin derivatives (22%), including prostacyclin, iloprost and epoprostenol.

DU analysis

DU varied widely within the LCOS subtypes, but the most commonly used drugs were typically reported for two or three subtypes. For initial treatment of LCOS, 21–39 different drug regimens were reported among all LCOS subtypes

(table 1). In total, 23, 16 and 22 drugs were used for LCOS with elevated SVR, low SVR and elevated PVR, respectively. These drugs belonged to nine different therapeutic drug classes (table 2). However, DU90% showed that 6–11 drugs from three to four therapeutic drug classes constituted the bulk of prescribing for all LCOS subtypes (figure 1A and table 2). Milrinone, epinephrine, dopamine and dobutamine were commonly reported for all subtypes and accounted for 54% of total drug use (figure 1B).

Table 3 Prescribing resources for low cardiac output syndrome

Sources of information for prescribing medicines	N (%)	95% CI
Standard hospital protocols	80 (41)	34 to 48
Product information sheets	33 (17)	12 to 23
Paediatric dosage handbooks*	24 (12)	8 to 18
National medicine compendia	21 (11)	7 to 16
Clinical pharmacist	18 (9)	6 to 14
Publications and medical databases	13 (7)	4 to 11
Experience and exchange with others	4 (2)	1 to 5
Standard textbooks	3 (2)	1 to 4

Participants were asked which resources they use daily for prescribing. Response options provided were: standard protocols in your hospital, product information sheets, national medicine compendium, the *British National Formulary for Children (BNF-C)*, clinical pharmacist and other (please specify). Multiple answers were possible. 196 responses were provided.
*Paediatric dosage handbooks includes reports mentioning the *BNF-C* (15 reports), *Drug Doses* by F Shann (6), *Handbook of Pediatric Cardiovascular Drugs* by R Munoz *et al*, (1), *Pediatric Dosage Handbook* by CK Taketomo (1) and Great Ormond Street Hospital CICU Protocol (1).

Sources of information for prescribing

A substantial number of participants reported that currently available drug and dosing information was not sufficient for effectively prescribing medicines for children with OHS. In all, 36 out of 90 participants (40%, 95% CI 30% to 50%) stated the level of information was not sufficient, while 51 out of 90 participants (57%, 95% CI 46% to 66%) believed it was sufficient. Three participants were indecisive (3%, 95% CI 1% to 9%). Standard hospital protocols were mostly consulted for prescribing (table 3).

Furthermore, the majority of participants (N=79) voted in favour of clinical practice guidelines in this setting (88% vs 4%, 95% CI 79% to 93% vs 2% to 11%). Seven participants (8%, 95% CI 4% to 15%) were unsure.

DISCUSSION

This survey summarises current hospital practice related to drug treatment for LCOS in children with OHS in Europe, which is characterised by high variability in drug use for LCOS with elevated and low SVR, and elevated PVR (table 1). Despite this variability, 6–11 drugs constitute 90% of total drug use for all LCOS subtypes, with milrinone, epinephrine, dopamine and dobutamine most commonly reported for all subtypes (figure 1). Moreover, the survey results reveal that 40% of participants deem currently available prescribing resources insufficient.

The survey suggests that variability is the primary characteristic of drug treatment for LCOS in children. Significant concordance among hospitals was identified only for initial treatment

Table 4 Comparison between preferred treatment algorithms for LCOS subtypes in EuLoCOS-Paed and guideline recommendations

		Survey	Guidelines			
Indication	Step	EuLoCOS-Paed[a] (2011)	Congenital heart disease[b17] (2000)	Surviving sepsis campaign[a6] (2008)	Septic shock – paediatrics[a5] (2009)	Septic shock – neonates[c5] (2009)
LCOS with elevated SVR[a], LV dysfunction[b], cold shock with poor LV function[c]	1	Milrinone	Dobutamine or dopamine	Dobutamine	Dobutamine	Dopamine+dobutamine
	2	Epinephrine	Epinephrine*	Epinephrine*	Epinephrine*	Epinephrine*
	3	Epinephrine or levosimendan	Milrinone, amrinone or nitroprusside	Vasodilator	Nitroprusside or glyceryl trinitrate	Nitrovasodilator or phosphodiesterase inhibitor
	4			Phosphodiesterase inhibitor	Milrinone or amrinone	
LCOS with low SVR[a]	1	Dopamine		Dopamine	Dopamine	
	2	Epinephrine		Norepinephrine	Epinephrine*	
	3	Norepinephrine		Vasopressin	Norepinephrine	
	4				Dobutamine, enoximone or levosimendan	
LCOS with elevated PVR[a], PHN[b], cold shock with RV dysfunction and PHN[c]	1	Milrinone	Inhaled nitric oxide			Dopamine+dobutamine
	2	Inhaled nitric oxide	Milrinone or amrinone			Epinephrine*
	3	Prostacyclin derivatives	Prostacyclin derivatives			Inhaled nitric oxide
	4					Milrinone, iloprost or adenosine
Grade/level of recommendation			Not reported	2C for dobutamine and dopamine†	2‡	2‡

Note: Superscripts in the first column a–c indicate which survey and guidelines are referred to.
*Epinephrine may be used for dobutamine or dopamine resistant shock.
†Guideline development was based on the GRADE system, which classifies the quality of evidence as high (grade A), moderate (grade B), low (grade C) or very low (grade D). Recommendations are classified as strong (grade 1) or weak (grade 2).
‡Guideline development was based on the American College of Critical Care Medicine guidelines for an evidence-based medicine rating system, which assesses the strength of recommendation as "'convincingly justifiable on scientific evidence alone"' (level 1), "'reasonably justifiable by scientific evidence and strongly supported by expert critical care opinion"' (level 2) and "'adequate scientific evidence is lacking but widely supported by available data and expert opinion'" (level 3).
LCOS, low cardiac output syndrome; LV, left ventricular; PHN, pulmonary hypertension; PVR, pulmonary vascular resistance; RV, right ventricular; SVR, systemic vascular resistance.

of LCOS with elevated SVR, with milrinone monotherapy being reported by 34% of participants (table 1).

Until now, the only comparative surveys were for adult patients, which also indicated that drug use is variable within and across European countries, although seemingly less so than in the present survey. Kastrup *et al*[16] showed that 42% of German clinicians select epinephrine from eight drug options as the first-choice drug for adult patients with LCOS, 91% of French clinicians select dobutamine from four drug options for cardiogenic shock[15] and 64% of clinicians from Scandinavia select dopamine for cardiac failure.[14] The present survey probably revealed higher variability in drug use because it focussed on children and hospitals from all over Europe, and also subcategorised LCOS and evaluated stepwise treatment algorithms without limiting drug choices. Therefore, this survey may contribute to a more complete understanding of LCOS treatment.

One reason for the variable pattern of drug use identified in this survey may be the lack of sufficient evidence from well-conducted clinical trials in children with LCOS, which limits the strength of recommendations. This is reflected in two current septic shock guidelines addressing drug treatment for LCOS in children.[5 6] To use the example of LCOS with elevated SVR, guidelines favour dobutamine as a first-line drug for children, but this is only supported by low grade evidence (grade C) from observational studies.[6] Consequently, its use is weakly recommended and should be considered 'according to particular circumstances'.

Contrary to guidelines for LCOS with elevated SVR, European clinicians tend to initiate drug treatment with milrinone (table 1). Guidelines recommend milrinone as a second- or third-line drug (table 4).[5 6 17] We can only speculate that milrinone's favourable effect on cardiac index and SVR, with less effect on heart rate compared to dobutamine, explains its more frequent use in children.[28–30] This pattern of drug use also differs from that in adult patients, where milrinone has been largely replaced by levosimendan for acute heart failure and cardiogenic shock.[31] In adult patients, levosimendan is recommended for the prevention and treatment of postcardiopulmonary bypass LCOS.[32] Limited study data on levosimendan in children,[33] high treatment costs and marketing authorisation in only selected European countries may explain why it is used in less than 10% of children with LCOS and elevated SVR. Overall, there are insufficient data from well-conducted comparative clinical trials in children to inform decisions on which drugs produce the optimum risk-benefit ratio in children.

The drugs which most need research in this setting are the 6–11 drugs that constitute 90% of total drug use for all LCOS subtypes. More importantly, milrinone, epinephrine, dopamine and dobutamine were used by half of the survey participants for all LCOS subtypes (figure 1), providing solid grounds for future research. This confirms and expands upon the findings of the European Medicines Agency and the US National Institutes of Health decision papers on drugs most in need of study in children, which refer to the recognised need for efficacy and safety data for dobutamine, dopamine and milrinone.[34 35] This is especially important considering their potentially harmful effects in critically ill patients.[36–38] However, the present survey results also indicate that epinephrine may similarly demand critical evaluation in children, which has not yet been captured on the official lists.

Drug treatment of LCOS is constrained by insufficient drug and dosing guidance as highlighted by 40% of respondents. These results are in keeping with a recent study on prescribing habits in a large paediatric teaching hospital in the USA[39] showing that 66% of attending physicians and physician fellows consider that the availability of dosing guidance is only 'somewhat convenient'. For LCOS, dobutamine is the only drug licensed for children in two European countries[8] but there are still significant gaps in its labelling. The Summary of Product Characteristics[40] gives a 15-fold range in dosing while pointing simultaneously to the narrow therapeutic index of dobutamine in children. Efficacy data are lacking in neonates.[34] Consequently, the survey participants are correct in highlighting the need for research, which may ultimately lead to more drugs having paediatric labelling and ensure their safety, efficacy and quality in children with LCOS.

The survey was constrained by its reliance on self-reported measures of clinicians' practice behaviours. However, two facts support the validity and reliability of the results. First, the final response rate of 72% provided by an equal mix of specialists in the care of children with OHS ensures that the results are reproducible, the risk of selection bias is minimised and the validity of the results is enhanced.[22] Second, the questionnaire was distributed via email by an institute not affiliated with the hospitals, which further reduces bias.[41] Another limitation was that the questionnaire did not determine other support measures for LCOS; it also did not stratify drug use with regard to cardiac malformation, severity of illness or patient's age. Therefore, the survey results may be regarded as a general approach to drug treatment for LCOS. In addition, the questionnaire did not enquire about dosing information regarding LCOS treatment due to practical time constraints for filling in the questionnaire and the need to ensure a survey response rate high enough so that the results would be representative of European clinical practice. However, dosing information was queried in the third section of this questionnaire regarding drug use for LCOS prevention and the results previously published.[12 13] Hopefully, the survey results will trigger further work in this field.

In summary, these survey results present current hospital practice with regard to drug treatment of LCOS in children with OHS in Europe. This is characterised by highly variable drug use and insufficient drug and dosing information. The value of the survey in deciding which drugs most need research in this setting is evident. Milrinone, epinephrine, dopamine and dobutamine were identified as the principal drugs used for all LCOS subtypes. Therefore, prioritising critical evaluation of the safety and efficacy of these drugs in children with LCOS could allow targeted use of healthcare resources and quickly and effectively improve the quality of drug use in Europe.

Contributors Both authors contributed to the conception and design of the survey, the analysis and interpretation of data, to the drafting of the manuscript andor revising it critically revision for important intellectual content; both gave final approval of the manuscript submitted.

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REFERENCES

1. **Hoffman TM**, Wernovsky G, Atz AM, *et al*. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation* 2003;**107**:996–1002.
2. **Shi S**, Zhao Z, Liu X, *et al*. Perioperative risk factors for prolonged mechanical ventilation following cardiac surgery in neonates and young infants. *Chest* 2008;**134**:768–74.

3. **Ma M**, Gauvreau K, Allan CK, *et al*. Causes of death after congenital heart surgery. *Ann Thorac Surg* 2007;**83**:1438–45.
4. **Roth SJ**, Adatia I, Pearson GD. Summary proceedings from the cardiology group on postoperative cardiac dysfunction. *Pediatrics* 2006;**117**:S40–6.
5. **Brierley J**, Carcillo JA, Choong K, *et al*. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med* 2009;**37**:666–88.
6. **Dellinger RP**, Levy MM, Carlet JM, *et al*. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008;**36**:296–327.
7. **Yoon EY**, Davis MM, El-Essawi H, *et al*. FDA labeling status of pediatric medications. *Clin Pediatr (Phila)* 2006;**45**:75–7.
8. European Medicines Agency. Assessment of the Paediatric Needs – Cardiovascular Products. 2006. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004057.pdf (accessed 21 April 2011).
9. **Pasquali SK**, Hall M, Li JS, *et al*. Corticosteroids and outcome in children undergoing congenital heart surgery: analysis of the Pediatric Health Information Systems database. *Circulation* 2010;**122**:2123–30.
10. **Turner S**, Nunn AJ, Fielding K, *et al*. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatr* 1999;**88**:965–8.
11. **Maltz LA**, Klugman D, Wessel DL. Off-label drug use in a single center pediatric cardiac intensive care unit. Presented at the American Academy of Pediatrics (AAP) National Conference and Exhibition, 17–20 October 2009, Washington, DC.
12. **Vogt W**, Läer S. Drug use patterns for the prevention of paediatric low cardiac output syndrome in Europe. *Intensive Care Med* 2011;**37**:1390–1.
13. **Vogt W**, Läer S. Prevention for paediatric low cardiac output syndrome: results from the European survey EuLoCOS-Paed. *Pediatr Anesth* 2011;(In Press) doi: 10.1111/j.1460-9592.2011.03683.x.
14. **Oldner A**, Rossi P, Karason S, *et al*. A practice survey on vasopressor and inotropic drug therapy in Scandinavian intensive care units. *Acta Anaesthesiol Scand* 2003;**47**:693–701.
15. **Leone M**, Vallet B, Teboul JL, *et al*. Survey of the use of catecholamines by French physicians. *Intensive Care Med* 2004;**30**:984–8.
16. **Kastrup M**, Markewitz A, Spies C, *et al*. Current practice of hemodynamic monitoring and vasopressor and inotropic therapy in post-operative cardiac surgery patients in Germany: results from a postal survey. *Acta Anaesthesiol Scand* 2007;**51**:347–58.
17. **Baño Rodrigo A**, Domínguez Pérez F, Fernández Pineda L, *et al*. [Practice Guidelines of the Spanish Society of Cardiology in the postoperative course of congenital heart diseases]. *Rev Esp Cardiol* 2000;**53**:1496–526.
18. **Carl M**, Alms A, Braun J, *et al*. [Guidelines for intensive care in cardiac surgery patients: haemodynamic monitoring and cardio-circulatory treatment guidelines of the German Society for Thoracic and Cardiovascular Surgery and the German Society of Anaesthesiology and Intensive Care Medicine]. *Thorac Cardiovasc Surg* 2007;**55**:130–48.
19. **Dillman DA**. *Mail and Internet Surveys: The Tailord Design Method*. 2nd edition. Hoboken, NJ: John Wiley & Sons 2007.
20. **Lumsden J**. Guidelines for the Design of Online Questionnaires: 1st Edition. Ottawa, ON: National Research Council Canada, 2005.
21. **Presser S**, Blair J. Survey pretesting: do different methods produce different results. *Sociol Methodol* 1994;**24**:73–104.
22. **Burns KE**, Duffett M, Kho ME, *et al*. A guide for the design and conduct of self-administered surveys of clinicians. *CMAJ* 2008;**179**:245–52.
23. **Carcillo JA**, Piva JP, Thomas NJ, *et al*. Shock and shock syndromes. In: Slonim A, Pollack M, Bell MJ, Berger J, Carcillo JA, eds. *Pediatric Critical Care Medicine*. Philadelphia, PA: Lippincott Williams and Wilkins 2006:438–71.
24. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2011. 2011. http://www.whocc.no/ (accessed 18 April 2011).
25. **Altman DG**, Machin D, Bryant TN, *et al*. *Statistics with Confidence*. 2nd edition. Bristol: BMJ Books 2000.
26. **Bergman U**, Popa C, Tomson Y, *et al*. Drug utilization 90% – a simple method for assessing the quality of drug prescribing. *Eur J Clin Pharmacol* 1998;**54**:113–8.
27. National Research Ethics Service. Defining Research. NRES Guidance to Help You Decide If Your Project Requires Review by a Research Ethics Committee 2009. http://www.nres.npsa.nhs.uk/applications/guidance/ (accessed 28 July 2010).
28. **Barton P**, Garcia J, Kouatli A, *et al*. Hemodynamic effects of i.v. milrinone lactate in pediatric patients with septic shock. A prospective, double-blinded, randomized, placebo-controlled, interventional study. *Chest* 1996;**109**:1302–12.
29. **Kwapisz MM**, Neuhäuser C, Scholz S, *et al*. Hemodynamic effects of dobutamine and dopexamine after cardiopulmonary bypass in pediatric cardiac surgery. *Paediatr Anaesth* 2009;**19**:862–71.
30. **Bohn DJ**, Poirier CS, Edmonds JF, *et al*. Hemodynamic effects of dobutamine after cardiopulmonary bypass in children. *Crit Care Med* 1980;**8**:367–71.
31. **Nieminen MS**, Brutsaert D, Dickstein K, *et al*. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;**27**:2725–36.
32. **Carl M**, Alms A, Braun J, *et al*. S3 guidelines for intensive care in cardiac surgery patients: hemodynamic monitoring and cardiocirculary system. *Ger Med Sci* 2010;**8**:1–25.
33. **Momeni M**, Rubay J, Matta A, *et al*. Levosimendan in congenital cardiac surgery: a randomized, double-blind clinical trial. *J Cardiothorac Vasc Anesth* 2011;**25**:419–24.
34. European Medicines Agency. Revised Priority List for Studies into Off-Patent Paediatric Medicinal Products for the 5th Call 2011 of the 7th Framework Programme of the European Commission. Revision 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004017.pdf (accessed 28 July 2010).
35. National Institutes of Health. List of drugs for which pediatric studies are needed. Fed Regist 2003;68:2789–90.
36. **O'Connor CM**, Gattis WA, Uretsky BF, *et al*. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). *Am Heart J* 1999;**138**:78–86.
37. **Cuffe MS**, Califf RM, Adams KF Jr, *et al*. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA* 2002;**287**:1541–7.
38. **Van den Berghe G**, de Zegher F. Anterior pituitary function during critical illness and dopamine treatment. *Crit Care Med* 1996;**24**:1580–90.
39. **Barrett JS**, Narayan M, Patel D, *et al*. Prescribing habits and caregiver satisfaction with resources for dosing children: rationale for more informative dosing guidance. *BMC Pediatr* 2011;**11**:25.
40. Summary of Product Characteristics. Dobutamin Liquid Fresenius 250 mg/50 ml Infusionslösung. Revision May 2008. http://www.fachinfo.de (accessed 1 April 2011).
41. **Adams AS**, Soumerai SB, Lomas J, *et al*. Evidence of self-report bias in assessing adherence to guidelines. *Int J Qual Health Care* 1999;**11**:187–92.

European Survey on the Pharmacological Management of Low Cardiac Output Syndrome in Children with Open Heart Surgery

- EuLoCOS-Paed -

I - Identifying sources of information for prescribing medicines for children with low cardiac output syndrome undergoing cardiac surgery with cardiopulmonary bypass

1) Do you think there is enough drug and dosing information available to prescribe in this field?
Please select one item from the list.

□ Yes
□ No
□ I am not sure (please specify):

2) Which resources do you use daily for prescribing?
Please select all items that apply to you.

□ Standard protocols in your hospital
□ Product information sheets
□ National medicine compendium
□ BNF-C (British National Formulary for Children)
□ Clinical pharmacist
□ Other (please specify):

3) Would you appreciate the availability of clinical practice guidelines?
Please select one item from the list.

□ Yes
□ No
□ I am not sure (please specify):

II - Pharmacological management for the treatment of low cardiac output syndrome in children undergoing cardiac surgery with cardiopulmonary bypass

4) Which drugs do you use for the initial management of LCOS associated with elevated systemic vascular resistance (fluid management already optimised)?
Please type in the name of the drug (Drug 1). If more than a single drug is used, please name the other drugs in the additional boxes (Drug 2, Drug 3).

	Drug 1	Drug 2	Drug 3
Initial therapy			

Web only figure 1 Questionnaire from the European Survey on the Pharmacological Management of Low Cardiac Output Syndrome in Children with Open Heart Surgery (EuLoCOS-Paed)

5) Which drugs do you add in the next two steps if the initial therapy is not sufficient?
Please type in the name of the add-on drug (Add-on drug 1). If more than a single add-on drug is used, please name the other drugs in the additional boxes (Add-on drug 2, Add-on drug 3). In case any drugs are discontinued, please indicate so in the comment box below.

	Add-on drug 1	Add-on drug 2	Add-on drug 3
First step			
Second step			

Comments

6) Which drugs do you use for the initial management of LCOS associated with low systemic vascular resistance (fluid management already optimised)?
Please type in the name of the drug (Drug 1). If more than a single drug is used, please name the other drugs in the additional boxes (Drug 2, Drug 3).

	Drug 1	Drug 2	Drug 3
Initial therapy			

7) Which drugs do you add in the next two steps if the initial therapy is not sufficient?
Please type in the name of the add-on drug (Add-on drug 1). If more than a single add-on drug is used, please name the other drugs in the additional boxes (Add-on drug 2, Add-on drug 3). In case any drugs are discontinued, please indicate so in the comment box below.

	Add-on drug 1	Add-on drug 2	Add-on drug 3
First step			
Second step			

Comments

8) Which drugs do you use for the initial management of LCOS associated with elevated pulmonary vascular resistance (fluid management already optimised)?
Please type in the name of the drug (Drug 1). If more than a single drug is used, please name the other drugs in the additional boxes (Drug 2, Drug 3).

	Drug 1	Drug 2	Drug 3
Initial therapy			

9) Which drugs do you add in the next two steps if the initial therapy is not sufficient?
Please type in the name of the add-on drug (Add-on drug 1). If more than a single add-on drug is used, please name the other drugs in the additional boxes (Add-on drug 2, Add-on drug 3). In case any drugs are discontinued, please indicate so in the comment box below.

	Add-on drug 1	Add-on drug 2	Add-on drug 3
First step			
Second step			

Web only figure 1 Questionnaire from the European Survey on the Pharmacological Management of Low Cardiac Output Syndrome in Children with Open Heart Surgery (EuLoCOS-Paed)

Comments

III - Pharmacological management for the prevention of low cardiac output syndrome in children undergoing cardiac surgery with cardiopulmonary bypass

10) Which paediatric patients do you provide with drugs for the prevention of low cardiac output syndrome?
Please select one item from the list.

□ All
□ Risk patients (please specify):
□ None

11) Which drugs do you use for the prevention?
Please type in the name of the drug and dosing regimen with the corresponding units. For drug combinations, please use the additional row.

	Drug name	Bolus dose	Duration of bolus administration	Maintenance dose	Duration of maintenance infusion
Drug 1					
Drug 2					

12) At which stage of the surgery do you use these drugs?
Please select all items that apply to you.

□ Perioperatively
□ Intraoperatively
□ Postoperatively

Comments

IV – Comments and feedback

Please add any additional comments or ideas that you consider relevant to this survey.

13) What is your speciality?
Please select one item from the list.

□ Anaesthesiology
□ Cardiothoracic surgery
□ Paediatric cardiology
□ Paediatric critical care medicine
□ Neonatal perinatal medicine
□ Clinical pharmacist

If your speciality is not listed, please specify here:

Web only figure 1 Questionnaire from the European Survey on the Pharmacological Management of Low Cardiac Output Syndrome in Children with Open Heart Surgery (EuLoCOS-Paed)

14) How many years of experience do you have caring for children with cardiopulmonary bypass surgery?
Please select one item from the list.

□ less than 1 year
□ 1 to 5 years
□ 5 to 10 years
□ more than 10 years

15) In which hospital are you working?
The information will be essential to see how many different hospitals and countries contributed to the results. Please remember that all your answers will be kept confidential.

Name of the hospital
City
Country

Web only figure 1 Questionnaire from the European Survey on the Pharmacological Management of Low Cardiac Output Syndrome in Children with Open Heart Surgery (EuLoCOS-Paed)

Web only table 1 Classification of drugs reported with respect to their therapeutic drug classes for the analysis of the EuLoCOS-Paed reports

Inotropes	Vasodilators	Inodilators	Vasopressors	Inovasopressors	Corticosteroids	Analgesics and anesthetics	Agents acting on the renin-angiotensin system	Muscle relaxants
Calcium[a]	Bosentan[b]	Amrinone[c]	Desmopressin[d]	Dopamine[c]	Dexamethason	Fentanyl	Enalapril	Pancuronium
Dobutamine[c]	Fenoldopam[e]	Enoximone[c]	Methylene-blue[f]	Norepinephrine[c]	Hydrocortison	Morphine		
Epinephrine[c]	Glyeryl trinitrate[c]	Isoprenalin[c]	Phenylephrine[c]		Methylprednisolon	Remifentanil		
	Inhaled nitric oxide[e]	Levosimendan[c]	Terlipressin[g]			Sevoflurane		
	Isosorbide dinitrate[h]	Milrinone[c]	Vasopressin[c]			Thiopental		
	Nitroprusside[c]	Theophylline[i]						
	Phenoxybenzamine[c]							
	Phentolamine[j]							
	Prostacyclin derivatives[c]							
	Prostaglandin[c]							
	Sildenafil[b]							
	Urapidil[k]							
	Vasodilator				Steroids	Sedation	Angiotensin-converting enzyme inhibitors	Neuromuscular-blocking drugs

Cardiovascular drugs were classified according to Carcillo [23] into inotropes, vasodilators, inodilators, vasopressors, and inovasopressors. Since angiotensin-converting enzyme inhibitors, corticosteroids, analgesics and anesthetics, and muscle relaxants are not included in this classification, they were grouped separately according to the second level, i.e. therapeutic subgroup, of the Anatomical Therapeutic Chemical (ATC) classification system [24]. Few drug entries were general, i.e. vasodilator (1 report), steroids (1), sedation (1), angiotensin-converting enzyme inhibitors (3) and neuromuscular-blocking drugs (1). Prostacyclin derivatives included reports with PGI2, iloprost and epoprostenol

Cited references for the classification of cardiovascular drugs into the therapeutic drug classes:
[a] Critical heart disease in infants and children. 2nd ed. Philadelphia, PA: Mosby Elsevier; 2006. pp. 173–203; [b] Hill et al. Respir Care 2009;54(7):958–68; [c] Pediatric Critical Care Medicine. 1st ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006. pp. 438-47; [d] Mignani et al. Minerva Anestesiol 2002;68(11):855-7, 858-9; [e] Hammer et al. BMC Anesthesiol 2008;8:6; [f] Lavigne et al. Semin Cardiothorac Vasc Anesth 2010;14(3):186–9; [g] Lange et al. Intensive Care Med 2008;34(5):821–32; [h] Muikku et al. Br J Anaesth 1992;68(4):376–80; [i] Scholz. J Am Coll Cardiol 1984;4(2):389–97; [j] Majid. Lancet 1971;2(7727):719–24; [k] Buch. Adv Ther 2010;27(7):426–43.

Chapter 3

PREVENTING PAEDIATRIC LOW CARDIAC OUTPUT SYNDROME

Chapter 3.1

PREVENTION FOR PEDIATRIC LOW CARDIAC OUTPUT SYNDROME: RESULTS FROM THE EUROPEAN SURVEY EULOCOS-PAED

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Prevention for pediatric low cardiac output syndrome: results from the European survey EuLoCOS-Paed

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Summary

Objective: Characterize current hospital practices related to preventive drug therapy for low cardiac output syndrome (LCOS) in children with open heart surgery (OHS) in Europe.
Methods: Web-based questionnaire survey of European hospitals performing OHS in children, conducted between January and August 2009.
Results: Responses to the questionnaire were obtained from 90 of 125 hospitals (72.0%) from 31 different countries across the geographical European regions. The majority of hospitals (77.8%) administered preventive drug therapy and primarily targeted patients at risk (63.3%). Twenty-four different drug regimens were reported, involving 17 drugs from seven therapeutic drug classes. Milrinone, dopamine, epinephrine, dobutamine, and levosimendan made up 85.9% of the total drug use. Furthermore, milrinone was reported in 70.7% of all drug regimens and significantly more often in combination with other drugs than monotherapy (Δ20%, 95% CI 4.7–34.1%). Milrinone combination therapy reports included lower bolus but higher maintenance infusion doses than monotherapy reports. The timing of drug regimen administration varied across the full perioperative period, but drug regimens were mostly initiated during surgery and continued postoperatively.
Conclusion: Although current hospital practices related to preventive drug therapy for LCOS in children with OHS are characterized by a marked variability, only few drugs make up the bulk of prescribing practice with milrinone being most commonly used. Therefore, the survey provides information on which drugs to focus research and establish safe and effective drug use. A unified approach is urgently needed to ensure that children with OHS can benefit from evidence-based care.

Introduction

With a birth prevalence of approximately 0.8%, congenital heart defects represent the most common congenital disorders in newborns (1). Approximately half of these children require cardiac surgery within the first year of life to ensure survival. Children with more severe defects undergo open heart surgery (OHS) with the risk of developing low cardiac output syndrome (LCOS). LCOS is a clinical condition caused by a temporary drop in systemic perfusion because of myocardial dysfunction and typically observed 6–18 h after OHS (2,3). Because LCOS is associated with increased morbidity (3) and mortality (4), healthcare professionals have turned their attention to preventive strategies for LCOS involving the administration of drugs.

However, no guideline exists to support clinicians' choices for preventive drug therapy for LCOS in children; similarly, the efficacy and safety data on the vasoactive drugs used to combat LCOS are insufficient. The evidence for the administration of preventive drug

therapy is mainly derived from the PRophylactic Intravenous use of Milrinone After Cardiac OpeRation in Pediatrics (PRIMACORP) study (3) reporting a significant relative risk reduction in LCOS after administration of high-dose milrinone (75 $\mu g \cdot kg^{-1}$ and 0.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$) but not low-dose milrinone (25 $\mu g \cdot kg^{-1}$ and 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) compared to placebo in children <6 years old with OHS. However, besides a single-center study in a Canadian hospital on the use of milrinone in critically ill children with a mixed focus on LCOS prevention and treatment (5), there is little information available with which to evaluate the current drug use for LCOS prevention in children.

Therefore, we conducted a pan-European survey to characterize current hospital practices related to preventive drug therapy for LCOS in children with OHS. Results on dosing and duration of drug administration for the drugs reported for LCOS prevention were published in (6). Here, we present a detailed description of the survey participants, the target patient group for LCOS prevention and the drug regimens reported. The results may guide the targeting of the drugs with the greatest need of research in this setting and promote safe and effective drug use in children with OHS.

Methods

Survey instrument

The questionnaire was developed after analyzing previous surveys on vasoactive drug use in adult patients (7,8) and guidelines on cardiac and circulatory failure (9–11). Standard survey methods for mail and web-based surveys were adopted to increase the overall response rate (12). An expert panel consisting of nine European experts specializing in pediatric cardiology, anesthesiology, intensive care, cardiac surgery, and general medicine and two experts in survey design reviewed and pilot-tested the questionnaire. The survey design process is mapped in Figure S1.

The questionnaire (see Figure S2) consisted of 15 questions covering different aspects of drug therapy for LCOS in children with OHS. The questions on LCOS prevention concerned the target patient group, the drug regimens (monotherapy and/or combination therapy), and the mode of drug administration.

The questionnaire was designed to be completed in 5 min and enquired about routine prescribing practices in hospitals aiming for a response rate of at least 60–70% to ensure that the results were representative (12). Therefore, time-consuming questions regarding hospital performance were omitted. The questionnaire was integrated into a web-based survey platform (EFS Survey Version 6.0, Globalpark AG, Huerth, Germany).

Survey participants and administration

European countries from the 47 member states of the Council of Europe and Belarus with hospitals performing OHS were identified primarily from the European Association for Cardio-Thoracic Surgery Congenital Database. Clinicians received a personalized email inviting them to participate and providing the web link to the questionnaire. Reminder emails were sent after 2 and 4 weeks. Data were collected between January and August 2009.

Data grouping

To allow a therapeutic drug class analysis and make drug use comparable across countries, the drugs reported were grouped according to their therapeutic action. Cardiovascular drugs were classified according to Carcillo (13), corticosteroids and analgesics, and anesthetics were grouped separately according to the second level, i.e., therapeutic subgroup, of the Anatomical Therapeutic Chemical classification system (14) (see Table S1).

Data analysis

The drug regimens and individual drugs were analyzed by the number of times reported based on the generic drug name and the respective therapeutic drug class. The results were expressed as percentages and displayed with their 95% confidence intervals (CI), calculated using the Wilson method for single samples (15). Differences between two proportions were assessed on significance according to the confidence interval analysis for unpaired samples by Newcombe (15). To allow a comparison between different milrinone dosing strategies, density plots were created using the density {stats} command in the statistical software package R (R Foundation for statistical computing, Vienna, Austria). Within a dose range, reported doses were assigned equal weight by binning the dose ranges in 5 unit steps for the bolus and 0.05 unit steps for the maintenance infusion (e.g., for a dose range of 40–60 $\mu g \cdot kg^{-1}$, the bins 40, 45, 50, 55, and 60 would each receive one count).

Drug utilization (DU) was analyzed using the DU90% method as suggested by the WHO (16), in which drugs reported for each LCOS subtype and their respective therapeutic drug classes were combined and ranked in descending order according to their frequency of occurrence. DU90% refers to those drugs accounting for 90% of the total drug use and presents the bulk of prescribing.

Hospitals were excluded from the analysis if clinicians did not wish to participate, did not conduct OHS on children, or expressed a wish not to be included because of limited experience. Missing data were excluded from the frequency counts. Data analysis was performed with Microsoft® Office Excel 2003, R v. 2.12.1 (R Foundation for statistical computing), and CIA v. 2.1.2 (15) for the CI analysis.

Results

Survey participants

From 125 hospitals in 36 European countries eligible for inclusion in this questionnaire survey, 90 hospitals from 31 countries participated (Figure 1), yielding an overall response rate of 72.0%. The total number of hospitals performing OHS in children varied among countries; however, the response rate was comparable across the geographical regions in Europe except for southern Europe with the lowest response rate (55.3%).

The primary specialization of participants was pediatric cardiothoracic surgery, anesthesiology, intensive care, and cardiology (Table 1). Nearly all participants (94.4%) had at least 5-year experience in the care for children with OHS.

Target patient group for LCOS prevention

The responses to the questions asked in the questionnaire indicated that the administration of preventive drug therapy proved to be a common hospital practice in Europe. Seventy hospitals (77.8%) used preventive drug therapy, the majority of which selectively administered it to patients at risk (57 hospitals, 63.3%, 95% CI 53.3–72.6%). Only a small number of hospitals administered preventive drug therapy to all patients with OHS (13 hospitals, 14.4%, 95% CI 8.6–23.2%). In contrast, approximately one-fifth of the hospitals (20 hospitals, 22.2%, 95% CI 14.9–31.8%) omitted preventive drug therapy.

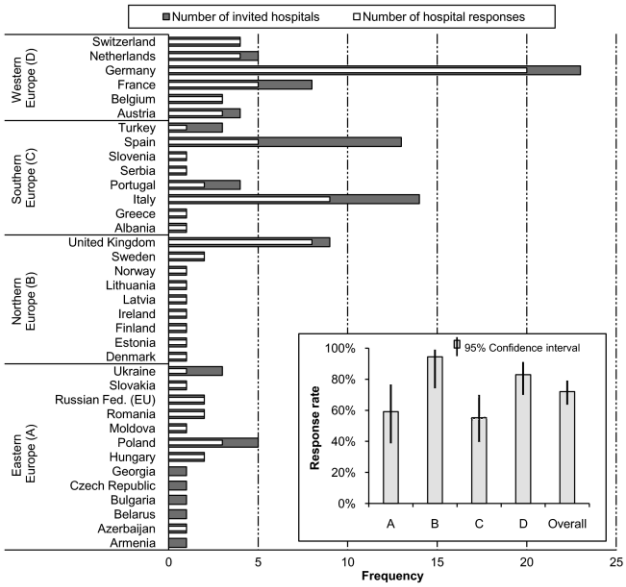

Figure 1 Description of the country participation in the survey. The number of invited eligible ($N = 125$) and responding ($N = 90$) hospitals per country ($N = 36$) is shown in Figure 1. Countries are grouped into eastern, northern, southern, and western Europe according to the United Nations Statistics Division – Geographical region and composition. Initially, 39 countries with 130 hospitals performing open heart surgery (OHS) were identified and asked for study participation. Three countries with one hospital each were subsequently excluded from the analysis because OHS in children was performed outside the country. In addition, two further hospitals were excluded, one of which reported having only limited experience; another hospital did not wish to participate.

Table 1 Specialization of the survey participants and their experience in the care of children with open heart surgery

	n	(%)	95% CI
Specialization[a]			
Cardiothoracic surgery	29	28.4	20.6–37.8
Anesthesiology	27	26.5	18.9–35.8
Intensive care	22	21.6	14.7–30.5
Cardiology	21	20.6	13.9–29.4
Neonatology	1	1.0	0.2–5.3
Perfusion	1	1.0	0.2–5.3
Clinical pharmacist (intensive care)	1	1.0	0.2–5.3
Experience			
More than 10 years	73	81.1	71.8–87.9[b]
5–10 years	12	13.3	7.8–21.9
1–5 years	5	5.6	2.4–12.4
<1 year	0	0.0	0.0–4.1

[a]Multiple answers were possible.
[b]Significantly more often reported than others in this group.

The criteria for defining patients at risk, who received preventive drug therapy, differed among hospitals. The 55 responses provided by participants to the question 'Please specify patients at risk' could be grouped into five categories: patient requires complex cardiac surgery (30 responses for complex cardiac defects, one response for heart transplantation); patient has preexisting cardiac and/or pulmonary dysfunction (17 responses); surgery necessitates long bypass and/or cross-clamp time (12 responses); patient is young (five responses each for neonates and infants); and others including anesthetist assessment, redo-procedure, coronary problems during or after the surgery, and ischemic lesions (one response each).

Choice of drug regimens for LCOS prevention

Preventive drug therapy for LCOS was characterized by a marked variability. Twenty-four different drug regimens were identified from a total number of 75 responses by 69 hospitals. Four hospitals reported the use of at least two drug regimens, based on patient- and surgery-specific characteristics. One hospital reported the use of preventive drug therapy in general but did not fill in information on drug choice and was not included in this part of the analysis.

Of the 24 different drug regimens reported, milrinone monotherapy (25.3% of the reports) and a combination of milrinone with dopamine, epinephrine, dobutamine, or levosimendan were mostly used and made up 64.0% of all reports (Table 2). The drug regimens were mostly initiated during surgery and continued postoperatively, but covered overall the full perioperative period.

Table 2 Reports on drug use for low cardiac output syndrome prevention: mode of drug use, drug regimens, and timing of drug administration

	n (risk/all)[a]	(%)	95% CI
Mode of drug use			
Single-drug regimen	31 (25/6)	41.3	30.9–52.6
Two-drug regimen	43 (36/7)	57.3	46.1–67.9
Triple-drug regimen	1 (1/0)	1.3	0.2–7.2
Drug regimens[b]			
Milrinone	19 (15/4)	25.3	16.9–36.2
Milrinone + dopamine	9 (6/3)	12.0	6.4–21.3
Milrinone + epinephrine	8 (7/1)	10.7	5.5–19.7
Milrinone + dobutamine	7 (6/1)	9.3	4.6–18.0
Milrinone + levosimendan	5 (5/0)	6.7	2.9–14.7
Levosimendan	5 (5/0)	6.7	2.9–14.7
Therapeutic drug class regimens[b]			
Inodilator	25 (21/4)	33.3	23.7–44.6
Inodilator + inotrope	16 (14/2)	21.3	13.6–31.9
Inodilator + inovasopressor	10 (7/3)	13.3	7.4–22.8
Inodilator + inodilator	5 (5/0)	6.7	2.9–14.7
Inotrope	3 (1/2)	4.0	1.4–11.1
Inotrope + inovasopressor	3 (2/1)	4.0	1.4–11.1
Timing of administration (-operatively)			
Intra- and post-	43 (33/10)	57.3	46.1–67.9[c]
Pre-, intra- and post-	16 (15/1)	21.3	13.6–31.9
Intra-	6 (5/1)	8.0	3.7–16.4
Post-	6 (5/1)	8.0	3.7–16.4
Pre-	3 (3/0)	4.0	1.4–11.1
Pre- and intra-	1 (1/0)	1.3	0.2–7.2

The analysis was based on 75 reported drug regimens from 69 hospitals. Two hospitals provided three different drug regimens, and another two hospitals provided two drug regimens based on the underlying clinical condition of the patient and the type of open heart surgery. One hospital did not fill in the information on drug dosing.
[a]Refers to the total number of reports (*N*) and the frequency of being reported for 'patients at risk' and for 'all patients' (risk/all).
[b]Only the drug regimens and therapeutic drug class regimens that were reported more than twice are listed. Fourteen different drug regimens were reported only once, and four drug regimens were reported twice.
[c]Significantly more often reported than others in this group.

Individual drug analysis

Most of the preventive drug therapy involved a limited number of drugs. Of 17 different drugs in seven therapeutic drug classes (see Table S1) identified in the drug regimens reported, eight drugs in five therapeutic drug classes constituted 90% of the total drugs use, from which milrinone, dopamine, dobutamine, epinephrine, and levosimendan already made up 85.9% (Figure 2). In contrast, only one hospital report (0.8%) mentioned the use of vasopressors (i.e., phenylephrine).

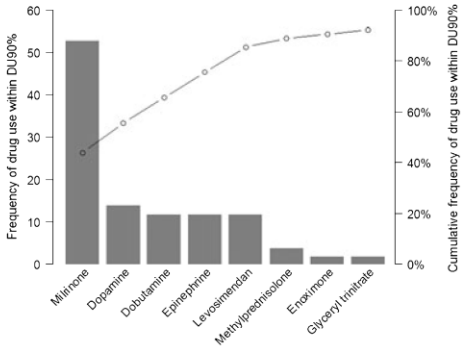

Figure 2 Frequency distribution of drug use for low cardiac output syndrome (LCOS) prevention within DU90%. DU90% refers to those drugs accounting for 90% of the total drug use, for which all drugs reported for the LCOS subtype ($N = 120$) were combined and ranked in descending order according to their frequency of reporting (16). In total, 8 of 17 drugs reported for LCOS prevention made up 90% of the total drug use, specifically 92.5%. The reason is that enoximone and glyceryl trinitrate were ranked seven with each 1.7% and, therefore, were both included into DU90%. The following drugs were reported once and accounted for the remaining 7.5% of drug use: alprostadil, bosentan, calcium, inhaled nitric oxide, nitroprusside, norepinephrine, phenoxybenzamine, phenylephrine, and thiopental. Data on how the individual drugs were used, i.e., monotherapy or combination therapy, can be found in Table 2.

Comparing milrinone mono- and combination therapy showed that milrinone was significantly more often used in combination with other drugs (Table 3) but its use was less variable in those hospitals where it was administered as the sole therapeutic agent for LCOS prevention. For milrinone monotherapy, more reports included a bolus dose (52.6% in the monotherapy group vs 38.2% in the combination therapy group), a maintenance infusion of ≤72 h (47.5% vs 32.4%), and a combined intra- and postoperative administration (78.9% vs 52.9%), albeit the lack of a significant difference between these proportions. Interestingly, hospitals would opt for lower bolus but higher maintenance infusion doses for milrinone when administered in combination with other drugs (Figure 3).

Discussion

The survey shows that preventive drug therapy for LCOS has become an integrated part of the perioperative management for children with OHS in the majority of European hospitals, but there is a marked variability in the way it is currently provided. Selection criteria to target patients at risk vary across the hospitals, as do the drug regimens used (Table 2). Nonetheless, among the 24 different drug regimens reported, milrinone or its combination with dopamine, dobutamine, epinephrine, and levosimendan was used in 64.0% of the reports rendering milrinone the drug of choice for LCOS prevention in Europe. Milrinone was mostly initiated in the operating theater at a median dose of 50 $\mu g \cdot kg^{-1}$ followed by 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which differs from the dosing regimen that proved beneficial for LCOS prevention in the PRIMACORP study (3).

Drugs play an important role in the prevention of LCOS in children with OHS. The present survey found that 77.8% of the European hospitals surveyed administered preventive drug therapy and targeted primarily pediatric patients at risk. There were differences among the practices of the European hospitals: some hospitals omitted prevention, while others did not undertake risk stratification and provided prevention to all patients with OHS. The targeted approach reported by 63.3% of the hospitals seems sensible, as no more than approximately one-quarter of the patients is affected by LCOS postoperatively (3) and these patients can be identified by risk parameters (17). Exposing all patients to preventive drug therapy may not only be associated with the risks of drug interactions and side effects in patients who do not experience therapeutic benefits but also with higher costs.

In contrast to the similarities among hospitals in terms of the patient group targeted, uniform risk stratification does not appear to exist. Different criteria were reported for selecting patients at risk, which partially overlap with those published by Carmona (17) for predicting LCOS in neonates and children with OHS. Carmona identified not only general patient and surgical characteristics but also specific inflammatory, metabolic, and cardiac markers, which were not reported by the survey participants. However, reporting bias cannot be excluded in the present survey, as the questionnaire item did not specifically determine hemodynamic and clinical criteria for the selection of patients at risk.

Results on dosing and duration of drug administration from this survey indicated a high variability in the drugs used for LCOS prevention in children across Europe as reported in (6). This is also true for the choice of drug regimens (Table 2). Surveys focusing on other aspects of medical care in children with OHS, such as the use of corticosteroids (18) and antibiotics (19), have also highlighted a variable pattern of drug use. This survey confirms the findings with regard to the variable medical care of children with OHS.

Table 3 Comparison of milrinone use between monotherapy and combination therapy reports

	Milrinone monotherapy (n = 19)[b]			Milrinone combination therapy (n = 34)[b]		
	n	(%)	95% CI	n	(%)	95% CI
Dosing[a]						
Bolus infusion						
Median (range)		50 μg·kg^{-1} (50–100)			50 μg·kg^{-1} (20–300)	
Maintenance infusion						
Median (range)		0.513 μg·kg^{-1}·min^{-1} (0.25–0.85)			0.50 μg·kg^{-1}·min^{-1} (0.2–1.5)	
Duration of drug administration						
Bolus infusion						
≤10 min	1	10.0	1.8–40.4	7	53.8	29.1–76.8
≤20 min	1	10.0	1.8–40.4	3	23.1	8.2–50.3
≤30 min	1	10.0	1.8–40.4	2	15.4	4.3–42.2
On bypass/prime	6	60.0	31.3–83.2	1	7.7	1.4–33.3
Not reported	1	10.0	1.8–40.4	0	0.0	0.0–22.8
Maintenance infusion						
≤24 h	2	10.5	2.9–31.4	4	11.8	4.7–26.6
≤48 h	3	15.8	5.5–37.6	5	14.7	6.4–30.1
≤72 h	4	21.1	8.5–43.3	2	5.9	1.6–19.1
≤96 h	0	0.0	0.0–16.8	2	5.9	1.6–19.1
≤120 h	1	5.3	0.9–24.6	2	5.9	1.6–19.1
≤144 h	1	5.3	0.9–24.6	0	0.0	0.0–10.2
≤168 h	1	5.3	0.9–24.6	0	0.0	0.0–10.2
As needed	3	15.8	5.5–37.6	10	29.4	16.8–46.2
Not reported	4	21.1	8.5–43.3	9	26.5	14.6–43.1
Timing of drug administration (-operatively)						
Intra- and post-	15	78.9	56.7–91.5[c]	18	52.9	36.7–68.5
Pre-, intra-, post-	2	10.5	2.9–31.4	9	26.5	14.6–43.1
Intra-	1	5.3	0.9–24.6	3	8.8	3.0–23.0
Post-	1	5.3	0.9–24.6	2	5.9	1.6–19.1
Pre-	0	0.0	0.0–16.8	2	5.9	1.6–19.1

[a]For milrinone monotherapy, 8 of 10 bolus and 18 of 19 maintenance infusion reports included a dose. For milrinone combination therapy, 12 of 13 bolus and 31 of 34 maintenance infusion reports included a dose.
[b]Significant proportional difference between the number of reports for milrinone mono- and combination therapy (Newcombe confidence interval analysis for unpaired samples): Δ20%, 95% CI 4.7–34.1%. The confidence interval analysis revealed no other significant proportional differences between milrinone mono- and combination therapy.
[c]Significantly more often reported than others in this group.

Despite the high number of different drug regimens reported in this Europe-wide survey, a detailed analysis revealed that LCOS prevention can be mainly described with only five drugs: milrinone, dopamine, epinephrine, dobutamine, and levosimendan making up 85.9% of the total drug use (Figure 2). Furthermore, milrinone was reported in 70.7% of all drug regimens (Table 3). This is in line with the survey results by Wernovsky *et al.* (20), who reported specifically on OHS for hypoplastic left heart syndrome and showed that milrinone was mostly used in children upon separation from cardiopulmonary bypass. Therefore, the results from both surveys acknowledge the importance of milrinone for preserving cardiac function in children with OHS in hospital practice (3,21).

The present survey contributes to a better understanding of milrinone use by providing evidence on current hospital practices across Europe and questioning specific practices with regard to their safety and efficacy for LCOS prevention. It was identified that milrinone is significantly more often co-administered with other vasoactive drugs and dosing differs between mono- and combination therapy (Tables 2 and 3; Figure 3). There is insufficient supportive evidence for either practice. Furthermore, the survey identified that the majority of hospitals use lower milrinone doses than suggested by PRIMACORP (3) and without the recommended bolus dose (22), which has been investigated by Gombotz *et al.* (21) demonstrating that levosimendan (0.1 μg·kg^{-1}·min^{-1}) and milrinone (0.5 μg·kg^{-1}·min^{-1}) equally preserved cardiac index in children < 1 year old. These findings may retrospectively provide evidence for the practice pattern in some European hospitals. Nonetheless, these findings do not

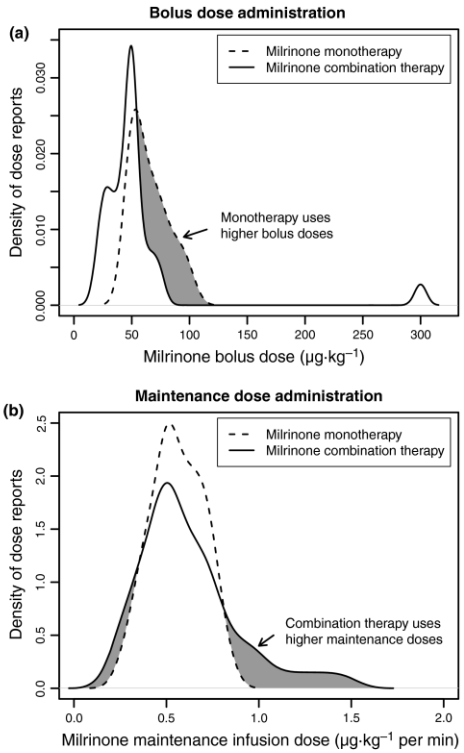

Figure 3 Density plots of milrinone bolus (a) and maintenance (b) dose reports comparing dosing strategies between milrinone mono- and combination therapy. Doses from within a dose range report were assigned equal weight by binning the dose ranges in 5 unit steps for the bolus and 0.05 unit steps for the maintenance infusion (e.g., for a dose range of 40–60 $\mu g \cdot kg^{-1}$, the bins 40, 45, 50, 55, and 60 would each receive one count). For milrinone monotherapy, 8 of 10 bolus and 18 of 19 maintenance infusion reports included a dose. For milrinone combination therapy, 12 of 13 bolus and 31 of 34 maintenance infusion reports included a dose. One hospital reported a bolus dose of three times 100 $\mu g \cdot kg^{-1}$ over a period of 2 min each, which was summarized as 300 $\mu g \cdot kg^{-1}$ for the analysis.

allow extrapolation of milrinone's dosing in terms of its efficacy and safety for older children, nor do they serve as an explanation for the wide dosing deviation identified in this survey.

Age-specific pharmacokinetic differences in the elimination of milrinone and fear of possible side effects, especially hypotension, may also explain the cautious dosing of milrinone and the frequent co-administration of drugs with vasopressor properties to counteract milrinone's vasodilatory effects as discussed in (6). However, it needs to be noted that PRIMACORP (3) showed no significant difference in the incidence of hypotension between treatment and placebo group; a prospective evaluation of the frequency and degree of hypotension under milrinone has yet to be undertaken to allow meaningful dose adjustments for LCOS prevention and ensure efficacy.

The survey results are limited by the reliance on self-reports by the participants. However, the final response rate of 72.0% and the equal mix of specialists in the care of children with OHS ensure the external validity and reliability of the results (12). In addition, the lack of guidelines in this field prevents physicians from being susceptible to biased responses (23), and lastly, the distribution of the questionnaire via email by an institute not affiliated with the hospitals further reduces bias (24). A limitation of the survey was that it did not specifically address the use of corticosteroids. Therefore, underreporting of corticosteroids in this survey is likely because they may not necessarily and exclusively be used for LCOS prevention. In addition, drug use was not stratified according to individual patient parameters, such as age, complexity of cardiac lesions, and preoperative cardiac functioning, and it may be possible that clinicians alter preventive drug therapy for LCOS thereupon despite the lack of supportive evidence. Therefore, the survey results should be regarded as a general approach toward LCOS prevention.

The implications from the survey results refer back to the Institute of Medicine's message that 'patients should receive care based on the best available scientific knowledge and care should not vary illogically from clinician to clinician or from place to place' (25). The present survey showed that preventive drug treatment for LCOS in children with OHS is highly variable and not backed by the necessary evidence for their efficacy and safety. In accordance with the European Medicines Agency (26), the aim should be to come to a consensus on a specific definition of LCOS (to know what to treat), to define the patient group that is likely to benefit most from preventive drug therapy (to know who to treat), and to establish safety, efficacy, and pharmacokinetic data for the drugs (to know how to treat). For such result-driven studies to be accomplished, various patient, concomitant disease, surgical, cardiac monitoring, and drug-related parameters need to be considered including those criteria reported by the survey participants for selecting patients at risk to receive preventive drug therapy. In addition, choosing an appropriate primary end point,

which also meets criteria used by the regulative authorities in considering labeling changes, is paramount as discussed by Roth *et al*. (27).

In summary, this European survey characterizes preventive drug therapy for LCOS in children with OHS. With a response rate of 72.0%, the survey results are representative of current hospital practices in Europe. The findings highlight similarities in the patient group targeted but demonstrate that a uniform risk stratification scheme does not exist for children. There is also marked variability in the various preventive drug therapies, which differ from the evidence available. Nonetheless, the survey indicates that milrinone with or without an additional vasoactive drug seems to be first choice in Europe allowing a targeted approach to future clinical research and establishing safe and effective drug use for LCOS prevention in children with OHS.

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Conflict of interest

No conflicts of interest declared.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Mapping of the survey design, questionnaire development and administration.

Figure S2. Questionnaire from the European Survey on the Pharmacological Management of Low Cardiac Output Syndrome in Children with Open Heart Surgery (EuLoCOS-Paed).

Table S1. Classification of the drugs reported with respect to their therapeutic drug classes.

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References

1 Moons P, Sluysmans T, De Wolf D *et al*. Congenital heart disease in 111 225 births in Belgium: birth prevalence, treatment and survival in the 21st century. *Acta Paediatr* 2009; **98**: 472–477.

2 Massé L, Antonacci M. Low cardiac output syndrome: identification and management. *Crit Care Nurs Clin North Am* 2005; **17**: 375–383.

3 Hoffman TM, Wernovsky G, Atz AM *et al*. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation* 2003; **107**: 996–1002.

4 Ma M, Gauvreau K, Allan CK *et al*. Causes of death after congenital heart surgery. *Ann Thorac Surg* 2007; **83**: 1438–1445.

5 Bishara T, Seto WT, Trope A *et al*. Use of milrinone in critically ill children. *CJHP* 2010; **63**: 420–428.

6 Vogt W, Läer S. Drug use patterns for the prevention of paediatric low cardiac output syndrome in Europe. *Intensive Care Med* 2011; **37**: 1390–1391.

7 Leone M, Vallet B, Teboul J *et al*. Survey of the use of catecholamines by French physicians. *Intensive Care Med* 2004; **30**: 984–988.

8 Kastrup M, Markewitz A, Spies C *et al*. Current practice of hemodynamic monitoring and vasopressor and inotropic therapy in post-operative cardiac surgery patients in Germany: results from a postal survey. *Acta Anaesthesiol Scand* 2007; **51**: 347–358.

9 Dellinger RP, Levy MM, Carlet JM *et al*. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; **36**: 296–327.

10 Brierley J, Carcillo JA, Choong K *et al*. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med* 2009; **37**: 666–688.

11 Carl M, Alms A, Braun J *et al*. Guidelines for intensive care in cardiac surgery patients: haemodynamic monitoring and cardio-circulatory treatment guidelines of the German Society for Thoracic and Cardiovascular Surgery and the German Society of Anaesthesiology and Intensive Care Medicine. *Thorac Cardiovasc Surg* 2007; **55**: 130–148.

12 Dillman DA. Mail and Internet Surveys: The Tailored Design Method, 2nd edn. Hoboken, NJ: John Wiley & Sons Inc, 2007.

13 Carcillo JA, Piva JP, Thomas NJ *et al*. Shock and shock syndromes. In: Slonim A, Pollack M, Bell MJ, Berger J, Carcillo JA, eds. Pediatric Critical Care Medicine. Philadelphia, PA: Lippincott Williams and Wilkins, 2006: 438–471.

14 WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2011; 2011. Available at: http://www.whocc.no/. Accessed 18 April, 2011.

15 Altman DG, Machin D, Bryant TN *et al*. Statistics with Confidence, 2nd edn. Bristol: BMJ Books, 2000.

16 Bergman U, Popa C, Tomson Y *et al*. Drug utilization 90% – a simple method for assessing the quality of drug prescribing. *Eur J Clin Pharmacol* 1998; **54**: 113–118.

17 Carmona F, Manso PH, Vicente WVA *et al*. Risk stratification in neonates and infants submitted to cardiac surgery with cardiopulmonary bypass: a multimarker approach combining inflammatory mediators, N-terminal pro-B-type natriuretic peptide and troponin I. *Cytokine* 2008; **42**: 317–324.

18 Allen M, Sundararajan S, Pathan N *et al*. Anti-inflammatory modalities: their current use in pediatric cardiac surgery in the United Kingdom and Ireland. *Pediatr Crit Care Med* 2009; **10**: 341–345.

19 Alphonso N, Anagnostopoulos PV, Scarpace S *et al*. Perioperative antibiotic prophylaxis in paediatric cardiac surgery. *Cardiol Young* 2007; **17**: 12–25.

20 Wernovsky G, Ghanayem N, Ohye RG *et al*. Hypoplastic left heart syndrome: consensus and controversies in 2007. *Cardiol Young* 2007; **17**(Suppl 2): 75–86.

21 Gombotz H, Lechner E, Hofer A *et al*. Levosimendan versus milrinone after biventricular corrective cardiac surgery. Presented at the 2010 Annual Meeting of the American Society of Anesthesiologists in San Diego, CA: October 16–20, 2010. Available at: http://www.asaabstracts.com/strands/asaabstracts/abstract.htm;jsessionid=0A69135BC5EA7FFE0ACAE8BAEC20A1AB?year=2010&index=16&absnum=642. Accessed 10 May, 2011.

22 Bailey JM, Hoffman TM, Wessel DL *et al*. A population pharmacokinetic analysis of milrinone in pediatric patients after cardiac surgery. *J Pharmacokinet Pharmacodyn* 2004; **31**: 43–59.

23 Nizami SQ, Khan IA, Bhutta ZA. Differences in self-reported and observed prescribing practice of general practitioners and paediatricians for acute watery diarrhoea in children of Karachi, Pakistan. *J Diarrhoeal Dis Res* 1995; **13**: 29–32.

24 Adams AS, Soumerai SB, Lomas J *et al*. Evidence of self-report bias in assessing adherence to guidelines. *Int J Qual Health Care* 1999; **11**: 187–192.

25 Committee on Quality of Health Care in America, Institute of Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century, 1st edn. Washington, DC: National Academies Press, 2001.

26 European Medicines Agency. Revised priority list for studies into off-patent paediatric medicinal products for the Fifth Call 2011 of the 7th Framework Programme of the European Commission, Rev. 2010 (Doc. Ref.: EMA/253396/2010). Accessed 28 July, 2010.

27 Roth SJ, Adatia I, Pearson GD *et al*. Summary proceedings from the cardiology group on postoperative cardiac dysfunction. *Pediatrics* 2006; **2**(3 Pt 2): S40–S46.

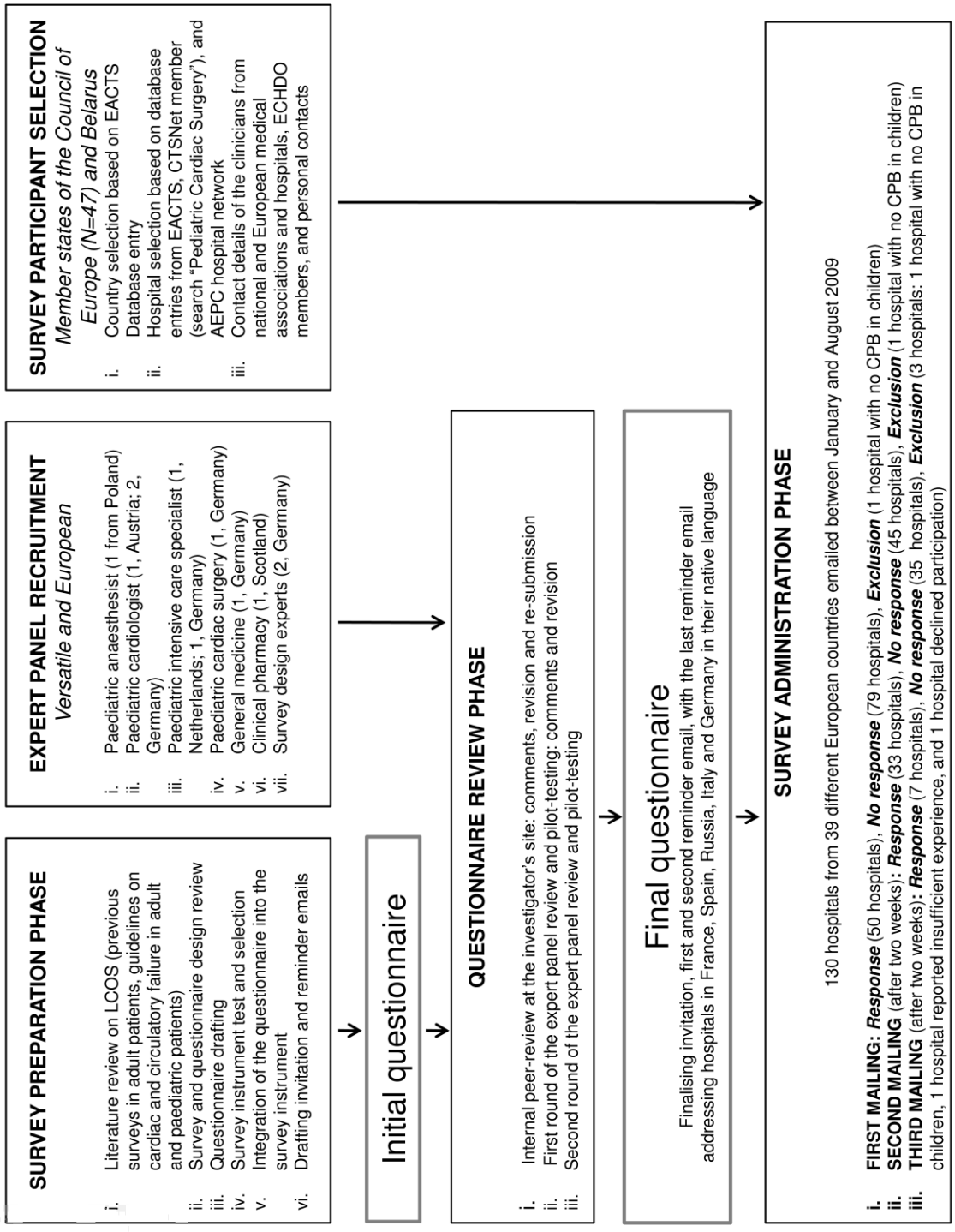

Figure S1 Mapping of the survey design, questionnaire development and administration

European Survey on the Pharmacological Management of Low Cardiac Output Syndrome in Children with Open Heart Surgery

- EuLoCOS-Paed -

I - Identifying sources of information for prescribing medicines for children with low cardiac output syndrome undergoing cardiac surgery with cardiopulmonary bypass

1) Do you think there is enough drug and dosing information available to prescribe in this field?
Please select one item from the list.

□ Yes
□ No
□ I am not sure (please specify):

2) Which resources do you use daily for prescribing?
Please select all items that apply to you.

□ Standard protocols in your hospital
□ Product information sheets
□ National medicine compendium
□ BNF-C (British National Formulary for Children)
□ Clinical pharmacist
□ Other (please specify):

3) Would you appreciate the availability of clinical practice guidelines?
Please select one item from the list.

□ Yes
□ No
□ I am not sure (please specify):

II - Pharmacological management for the treatment of low cardiac output syndrome in children undergoing cardiac surgery with cardiopulmonary bypass

4) Which drugs do you use for the initial management of LCOS associated with elevated systemic vascular resistance (fluid management already optimised)?
Please type in the name of the drug (Drug 1). If more than a single drug is used, please name the other drugs in the additional boxes (Drug 2, Drug 3).

	Drug 1	Drug 2	Drug 3
Initial therapy			

Figure S2 Questionnaire from the European Survey on the Pharmacological Management of Low Cardiac Output Syndrome in Children with Open Heart Surgery (EuLoCOS-Paed)

5) Which drugs do you add in the next two steps if the initial therapy is not sufficient?
Please type in the name of the add-on drug (Add-on drug 1). If more than a single add-on drug is used, please name the other drugs in the additional boxes (Add-on drug 2, Add-on drug 3). In case any drugs are discontinued, please indicate so in the comment box below.

	Add-on drug 1	Add-on drug 2	Add-on drug 3
First step			
Second step			

Comments

6) Which drugs do you use for the initial management of LCOS associated with low systemic vascular resistance (fluid management already optimised)?
Please type in the name of the drug (Drug 1). If more than a single drug is used, please name the other drugs in the additional boxes (Drug 2, Drug 3).

	Drug 1	Drug 2	Drug 3
Initial therapy			

7) Which drugs do you add in the next two steps if the initial therapy is not sufficient?
Please type in the name of the add-on drug (Add-on drug 1). If more than a single add-on drug is used, please name the other drugs in the additional boxes (Add-on drug 2, Add-on drug 3). In case any drugs are discontinued, please indicate so in the comment box below.

	Add-on drug 1	Add-on drug 2	Add-on drug 3
First step			
Second step			

Comments

8) Which drugs do you use for the initial management of LCOS associated with elevated pulmonary vascular resistance (fluid management already optimised)?
Please type in the name of the drug (Drug 1). If more than a single drug is used, please name the other drugs in the additional boxes (Drug 2, Drug 3).

	Drug 1	Drug 2	Drug 3
Initial therapy			

9) Which drugs do you add in the next two steps if the initial therapy is not sufficient?
Please type in the name of the add-on drug (Add-on drug 1). If more than a single add-on drug is used, please name the other drugs in the additional boxes (Add-on drug 2, Add-on drug 3). In case any drugs are discontinued, please indicate so in the comment box below.

	Add-on drug 1	Add-on drug 2	Add-on drug 3
First step			
Second step			

Comments

Figure S2 Questionnaire from the European Survey on the Pharmacological Management of Low Cardiac Output Syndrome in Children with Open Heart Surgery (EuLoCOS-Paed)

III - Pharmacological management for the prevention of low cardiac output syndrome in children undergoing cardiac surgery with cardiopulmonary bypass

10) Which paediatric patients do you provide with drugs for the prevention of low cardiac output syndrome?
Please select one item from the list.

□ All
□ Risk patients (please specify):
□ None

11) Which drugs do you use for the prevention?
Please type in the name of the drug and dosing regimen with the corresponding units. For drug combinations, please use the additional row.

	Drug name	Bolus dose	Duration of bolus administration	Maintenance dose	Duration of maintenance infusion
Drug 1					
Drug 2					

12) At which stage of the surgery do you use these drugs?
Please select all items that apply to you.

□ Perioperatively
□ Intraoperatively
□ Postoperatively

Comments

IV – Comments and feedback

Please add any additional comments or ideas that you consider relevant to this survey.

13) What is your speciality?
Please select one item from the list.

□ Anaesthesiology
□ Cardiothoracic surgery
□ Paediatric cardiology
□ Paediatric critical care medicine
□ Neonatal perinatal medicine
□ Clinical pharmacist

If your speciality is not listed, please specify here:

Figure S2 Questionnaire from the European Survey on the Pharmacological Management of Low Cardiac Output Syndrome in Children with Open Heart Surgery (EuLoCOS-Paed)

14) How many years of experience do you have caring for children with cardiopulmonary bypass surgery?
Please select one item from the list.

□ less than 1 year
□ 1 to 5 years
□ 5 to 10 years
□ more than 10 years

15) In which hospital are you working?
The information will be essential to see how many different hospitals and countries contributed to the results. Please remember that all your answers will be kept confidential.

Name of the hospital
City
Country

Figure S2 Questionnaire from the European Survey on the Pharmacological Management of Low Cardiac Output Syndrome in Children with Open Heart Surgery (EuLoCOS-Paed)

Table S1 Classification of the drugs reported with respect to their therapeutic drug classes

Therapeutic drug class	Drug
Analgesics and anesthetics	Thiopental
Corticosteroids	Methylprednisolone
Inodilators	Enoximone[a]
	Levosimendan[a]
	Milrinone[a]
Inotropes	Calcium chloride[b]
	Dobutamine[a]
	Epinephrine[a]
Inovasopressors	Dopamine[a]
	Norepinephrine[a]
Vasodilators	Alprostadil[a]
	Bosentan[c]
	Glyceryl trinitrate[a]
	Inhaled nitric oxide[a]
	Nitroprusside[a]
	Phenoxybenzamine[a]
Vasopressors	Phenylephrine[a]

Cardiovascular drugs were classified according to Carcillo (13) into inotropes, vasodilators, inodilators, vasopressors, and inovasopressors. Since corticosteroids, analgesics and anesthetics are not included in this classification, they were grouped separately according to the second level, i.e. therapeutic subgroup, of the Anatomical Therapeutic Chemical (ATC) classification system (14).

Cited references for the classification of cardiovascular drugs into the therapeutic drug classes:
[a] Pediatric Critical Care Medicine. 1st ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006. pp. 438-47.
[b] Critical heart disease in infants and children. 2nd ed. Philadelphia, PA: Mosby Elsevier; 2006. pp. 173–203.
[c] Hill et al. Respir Care 2009; 54 (7): 958–968.

Chapter 3.2

DRUG USE PATTERNS FOR THE PREVENTION OF PAEDIATRIC LOW CARDIAC OUTPUT SYNDROME IN EUROPE

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STEPHANIE LÄER

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IMPACT FACTOR 5.399

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Drug use patterns for the prevention of paediatric low cardiac output syndrome in Europe

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These results were presented in part at the 12th biannual congress of the European Society for Developmental Perinatal & Paediatric Pharmacology, in Chamonix, France in 2009.

Dear Editor,

Low cardiac output syndrome (LCOS) affects approximately 25% of children undergoing open heart surgery (OHS) and is associated with increased morbidity and mortality [1]. Evidence for preventive drug therapy for LCOS is derived primarily from the PRIMACORP study [1], which reported a reduction in LCOS risk after administration of high-dose milrinone, using a bolus of 75 μg/kg, followed by a maintenance infusion of 0.75 μg kg^{-1} min^{-1} over 35 h. Low-dose milrinone (25 μg/kg bolus and 0.25 μg kg^{-1} min^{-1} infusion) was not more effective than placebo. Other drugs may be also used but are not supported by safety and efficacy data [2, 3]. Data on drug use for LCOS prevention in children with OHS is not available for Europe. Therefore, the aim of this study was to characterise hospital practices related to preventive drug therapy for LCOS in children undergoing OHS as a basis for improving the standard of care in this setting.

A Web-based questionnaire was developed to survey 125 specialised hospitals from 36 European countries between January and August 2009. It included 15 questions allocated to 4 sections: prescribing resources and LCOS treatment (data not shown), LCOS prevention, and participant characteristics and comments. The questions on LCOS prevention enquired about the target patient group (all, at risk, none) and mode of drug administration, which was not further stratified. The hospitals were notified by email; of those, 90 hospitals from 31 countries responded (72.0% response rate). Respondents included clinicians (98.9%) and pharmacists (1.1%), specialising primarily in paediatric intensive care, anaesthesiology, cardiology, and cardiothoracic surgery. Nearly all respondents (94.4%) had at least 5 years of experience in caring for children undergoing OHS.

Most European hospitals (70 out of 90) reported preventive drug therapy for LCOS, from which the majority (57 hospitals) selectively targeted patients at risk. However, the drug use was highly variable. In total, 24 different drug regimens were reported, including 17 drugs from 7 therapeutic drug classes. Overall, 70.7% of the drug regimen reports included milrinone, making this the most commonly used drug. Dopamine, dobutamine, epinephrine, and levosimendan were reported significantly less often (Table 1). The dosage and duration of drug administration differed substantially among hospitals.

The results of this survey present the current pattern of drug use for LCOS prevention in children with

Table 1 Summary characteristics of the drugs commonly reported for LCOS prevention

Drug[a]	Frequency of drug use			Drug administration		
	N	%	95% CI	Bolus[b] (μg/kg)	Maintenance infusion[b] (μg kg^{-1} min^{-1})	Duration[b] (h)
Milrinone	53	70.7	59.6–79.8	50 (20–300)	0.5 (0.2–1.5)	39 (6–168)
Dopamine	14	18.7	11.5–28.9	–[c]	5 (0–15)	36 (8–72)
Dobutamine	12	16	9.4–25.9	7[d] (6–8)	5 (2–14)	36 (6–48)
Epinephrine	12	16	9.4–25.9	1 (1–1)	0.065 (0.003–0.3)	9 (6–12)
Levosimendan	12	16	9.4–25.9	12 (12–12)	0.15 (0.1–0.2)	24 (24–48)
Methylprednisolone	4	5.3	2.1–12.9	25[e] (10–35)	–	–

The analysis was based on 75 drug regimens reported from 69 hospitals. Two hospitals provided three different drug regimens and another two hospitals provided two drug regimens based on the clinical condition of the patient and the type of open heart surgery. One hospital did not fill in the information on drug dosing

[a] Only 6 out of 17 drugs were reported more than twice and are listed in the table. The following drugs were reported once or twice: alprostadil, bosentan, calcium, enoximone, glyceryl trinitrate, inhaled nitric oxide, norepinephrine, phenoxybenzamine, phenylephrine, nitroprusside, and thiopental

[b] Data are median with range in parenthesis

[c] Not reported

[d] Bolus dose in μg kg^{-1} min^{-1}

[e] Bolus dose in mg/kg

OHS across Europe, which is characterised by a marked variability. In addition, the dose of milrinone appears to be lower than that supported by PRIMACORP. Although our survey shows that milrinone is the most frequently used drug in Europe, neither the dosing nor the duration of drug administration coincide with those demonstrating efficacy in PRIMACORP (Table 1). Reasons for the reduced dose of milrinone may be attributable to concerns about potential side effects, especially hypotension [4], and the role of age-specific pharmacokinetic differences in the elimination of milrinone [5]. Nonetheless, these factors cannot explain the generally lower dose of milrinone used across all paediatric age groups, which needs to be addressed in future clinical research.

In summary, preventive drug therapy for LCOS in children undergoing OHS is highly variable across Europe, and the data available to support current hospital practices are insufficient. Given the importance of balancing benefits and risks with preventive drug therapy, this survey emphasises the need for further studies that will substantiate effective and safe LCOS prevention.

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References

1. Hoffman TM, Wernovsky G, Atz AM, Kulik TJ, Nelson DP, Chang AC, Bailey JM, Akbary A, Kocsis JF, Kaczmarek R, Spray TL, Wessel DL (2003) Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation 107:996–1002
2. Baldasso E, Garcia PCR, Piva JP, Branco RG, Tasker RC (2009) Pilot safety study of low-dose vasopressin in non-septic critically ill children. Intensive Care Med 35:355–359
3. Pasquali SK, Hall M, Li JS, Peterson ED, Jaggers J, Lodge AJ, Marino BS, Goodman DM, Shah SS (2010) Corticosteroids and outcome in children undergoing congenital heart surgery: analysis of the Pediatric Health Information Systems database. Circulation 122:2123–2130
4. Brierley J, Peters M (2006) Hemodynamics of milrinone loading in critically ill children. Crit Care Med 34:A63
5. Bailey JM, Hoffman TM, Wessel DL, Nelson DP, Atz AM, Chang AC, Kulik TJ, Spray TL, Akbary A, Miller RP, Wernovsky G (2004) A population pharmacokinetic analysis of milrinone in pediatric patients after cardiac surgery. J Pharmacokinet Pharmacodyn 31:43–59

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Chapter 4

OPTIMISING DRUG THERAPY FOR PAEDIATRIC LOW CARDIAC OUTPUT SYNDROME

EVALUATION AND OPTIMISATION OF CURRENT MILRINONE PRESCRIBING FOR THE TREATMENT AND PREVENTION OF LOW CARDIAC OUTPUT SYNDROME IN PAEDIATRIC PATIENTS AFTER OPEN HEART SURGERY USING A PHYSIOLOGY-BASED PHARMACOKINETIC DRUG-DISEASE MODEL

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ORIGINAL RESEARCH ARTICLE

Evaluation and Optimisation of Current Milrinone Prescribing for the Treatment and Prevention of Low Cardiac Output Syndrome in Paediatric Patients After Open Heart Surgery Using a Physiology-Based Pharmacokinetic Drug–Disease Model

Winnie Vogt

Abstract

Background and Objective Milrinone is the drug of choice for the treatment and prevention of low cardiac output syndrome (LCOS) in paediatric patients after open heart surgery across Europe. Discrepancies, however, among prescribing guidance, clinical studies and practice pattern require clarification to ensure safe and effective prescribing. However, the clearance prediction equations derived from classical pharmacokinetic modelling provide limited support as they have recently failed a clinical practice evaluation. Therefore, the objective of this study was to evaluate current milrinone dosing using physiology-based pharmacokinetic (PBPK) modelling and simulation to complement the existing pharmacokinetic knowledge and propose optimised dosing regimens as a basis for improving the standard of care for paediatric patients.

Methods A PBPK drug–disease model using a population approach was developed in three steps from healthy young adults to adult patients and paediatric patients with and without LCOS after open heart surgery. Pre- and postoperative organ function values from adult and paediatric patients were collected from literature and integrated into a disease model as factorial changes from the reference values in healthy adults aged 20–40 years. The disease model was combined with the PBPK drug model and evaluated against existing pharmacokinetic data. Model robustness was assessed by parametric sensitivity analysis. In the next step, virtual patient populations were created, each with 1,000 subjects reflecting the average adult and paediatric patient characteristics with regard to age, sex, bodyweight and height. They were integrated into the PBPK drug–disease model to evaluate the effectiveness of current milrinone dosing in achieving the therapeutic target range of 100–300 ng/mL milrinone in plasma. Optimised dosing regimens were subsequently developed.

Results The pharmacokinetics of milrinone in healthy young adults as well as adult and paediatric patients were accurately described with an average fold error of 1.1 ± 0.1 (mean ± standard deviation) and mean relative deviation of 1.5 ± 0.3 as measures of bias and precision, respectively. Normalised maximum sensitivity coefficients for model input parameters ranged from −0.84 to 0.71, which indicated model robustness. The evaluation of milrinone dosing across different paediatric age groups showed a non-linear age dependence of total plasma clearance and exposure differences of a factor 1.4 between patients with and without LCOS for a fixed dosing regimen. None of the currently used dosing regimens for milrinone achieved the therapeutic target range across all paediatric age groups and adult patients, so optimised dosing regimens were developed that considered the age-dependent and pathophysiological differences.

Conclusion The PBPK drug–disease model for milrinone in paediatric patients with and without LCOS after open heart surgery highlights that age, disease and surgery differently impact the pharmacokinetics of milrinone, and that current milrinone dosing for LCOS is suboptimal to maintain the therapeutic target range across the entire paediatric age range. Thus, optimised dosing strategies are proposed to ensure safe and effective prescribing.

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1 Introduction

Postoperative low cardiac output syndrome (LCOS) complicates the outcome of paediatric patients with open heart surgery for correction or palliation of congenital heart disease [1, 2]. To decrease the rate of morbidity and mortality associated with LCOS, the use of drugs is common practice and milrinone has been shown to be the drug of choice for LCOS treatment and prevention across Europe, although used off-label [3–5]. It was only in 2011/2012 that milrinone was approved across Europe for paediatric use following the conclusions of a European Public Assessment Report, so it is now indicated for LCOS treatment after open heart surgery in paediatric patients [6]. The use of milrinone for LCOS prevention, however, continues to be subject to off-label prescribing.

Despite the major step forward towards improved labelling of milrinone for paediatric use, discrepancies among prescribing guidance, evidence from clinical studies and clinical practice pattern need clarification to ensure safe and effective prescribing. Firstly, three pharmacokinetic studies in paediatric patients with open heart surgery [7–9] have identified an age dependency of the total plasma clearance of milrinone by applying classical, NONMEM approaches. However, this is not reflected by age-stratified dosing in the prescribing guidance. Second, despite the knowledge gained by applying the classical "top- down" modelling approach, a recent practice evaluation failed to predict plasma concentrations in paediatric patients with the available clearance prediction formula and highlighted the necessity to identify other explanatory parameters towards improved prediction of milrinone plasma concentrations in paediatric patients [10]. Lastly, the recommended dosing of milrinone for LCOS treatment in the Summary of Product Characteristics (SmPC) [11] is based on a regimen that has been shown to be safe and efficacious in paediatric patients without LCOS after open heart surgery, i.e. LCOS prevention [12]. However, differences in the disease status and organ function between patients with and without LCOS after surgery may differently impact the pharmacokinetics of milrinone, its safety and efficacy profile, and may render dose adaptation inevitable.

A systems-biology approach, such as physiology-based pharmacokinetic (PBPK) modelling, can support the necessary learning process towards optimised dosing by exploring relevant drug- and patient-specific parameters to explain the altered pharmacokinetics of milrinone in diseased patients as previously shown for other drugs in adult patients with liver disease [13, 14], renal disease [15, 16] and non-cardiac surgery [17]. Including the knowledge on organ growth and maturation in the system model also enables the prediction of drug exposure across different paediatric age groups [18–21]. Thus, PBPK drug–disease modelling provides the "bottom-up" approach to a mechanistic interplay between drug, disease, growth and maturation for all paediatric age groups to the extent of the available knowledge on physiology and pharmacology [22]. Hence, more informed decisions on paediatric drug dosing can be made and, by bridging adult and paediatric studies, the number of clinical trials in paediatric patients can be reduced [23]. This becomes especially true for rare clinical conditions, such as drug treatment for LCOS following paediatric open heart surgery. However, the lack of respective PBPK drug–disease models for adult and paediatric patients hampers the evaluation of current milrinone prescribing.

Therefore, the aim of this study was to employ a PBPK drug–disease modelling and simulation approach and develop a novel model to evaluate and optimise current milrinone prescribing for LCOS treatment and prevention in paediatric patients with open heart surgery. At the same time, the study would provide insight into the capabilities of systems biology modelling as an exploratory tool for improving drug dosing in paediatric patients.

2 Methods

With the aim of evaluating current milrinone prescribing for LCOS treatment and prevention in paediatric patients, a drug–disease model using a population PBPK approach was developed in three incremental steps: a drug model for milrinone in healthy young adults, which was then merged with a disease model reflective of the altered physiology and pathophysiology in adult patients with and without LCOS, and finally adapted to paediatric patients to describe age-dependent differences in physiology, pathophysiology and pharmacokinetics. Given successful model performance at each step of model development, as assessed by numerical and graphical evaluation, generic virtual patient populations were created representing the average paediatric and adult patients with open heart surgery, which were then simulated and the results used to evaluate and optimise current milrinone prescribing.

2.1 Development of the Physiology-Based Pharmacokinetic (PBPK) Drug–Disease Model

PK-Sim® (version 4.2, Bayer Technology Services, Leverkusen, Germany) was used for model development, which provides a generic whole-body PBPK modelling and simulation platform based on 17 organs and tissues to describe absorption, distribution, metabolism and excretion of compounds in humans. Each organ can be sub-divided into four compartments, which are plasma, red blood cells, interstitial and cellular space. Organ partition coefficients

and permeabilities are estimated from the compound's specific physico-chemical properties and the composition of tissues with respect to lipids, water and protein content [24].

2.1.1 Drug Model

The compound-specific parameters required for model building were retrieved from literature and summarised in Table 1. For plasma fraction unbound, the mean of the reported range of 9–30 % in the SmPC for milrinone [11] was used. In addition, hepatic and renal plasma clearances of milrinone were derived by non-compartmental analysis using PK-Solver [25] from plasma concentration–time profiles of intravenously administered milrinone to healthy male volunteers aged 20–40 years [26]. The renal plasma clearance of milrinone can be attributed to glomerular filtration and active tubular secretion as previously described [27]; however, no information is available on which enzymes are responsible for the hepatic clearance of milrinone, which is known to be mainly due to O-linked glucuronidation [28]. Consequently, O-linked glucuronidation was fully attributed to uridine diphosphate-glucuronosyltransferase 1A6 (UGT1A6) for model building because it is mainly involved in the O-linked glucuronidation of simple phenols [29, 30], which, in turn, have structural similarities to milrinone. This assumption was supported by the phase II enzyme prediction of ADMET Predictor™ (version 5.5.0005, Simulation Plus, Inc., Lancaster, CA, USA), which is based on the Artificial Neural Network Ensemble training methodology. The results from ADMET Predictor™ are shown in Table 2; they are supplemented with information on tissue expression site, substrate specificity and maximal specific activity [30].

Table 1 Input parameters for the physiology-based pharmacokinetic drug model

Parameter	Value	Variability	References
Physiochemical properties			
Molecular weight (g/mol)	211.22	NA	[100]
Lipophilicity (LogP)	0.42	NA	[101]
Plasma fraction unbound (%)	20	±10	[11]
pka-acid/base	4.5, 8.5	NA	[102]
Elimination			
Renal clearance (mL/min/kg)	5.12	GeoSD 1.2	[26]
Hepatic clearance (mL/min/kg)	1.08	GeoSD 1.7	[26]
Percentage blood flow increase due to milrinone			
Limbs	100	Physiological	[24, 37, 38]
Brain	20	Physiological	[24, 41]
Heart	38	Physiological	[24, 39]

GeoSD geometric standard deviation; *NA* not applicable

In the next step of model building, a descriptive function was established to quantify the contribution of renal plasma clearance of unchanged milrinone to total plasma clearance of milrinone, which is not fixed and depends on a patient's renal function as demonstrated by Woolfrey et al. [31] in patients with moderate to severe renal impairment. Consequently, bodyweight-normalised renal and total plasma clearance values of milrinone from patients with moderate to several renal impairment [31] were combined with the respective data from healthy young adults [26]; they were used to calculate milrinone's fraction excreted unchanged in urine (fe) for each subject, a marker of the renal contribution to total plasma clearance. fe was then plotted against the subject's creatinine clearance, which was used as a surrogate of the estimated glomerular filtration rate (eGFR) and assigned to the different stages of renal impairment according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guideline on chronic kidney disease [32]. Because creatinine clearance values were not available for healthy young adults, a set of random numbers with a mean and standard deviation (SD) of 119 ± 15 mL/min/1.73 m^2 were created in R (version 2.12.1, R Foundation for Statistical Computing, Vienna, Austria) to reflect eGFR in healthy adults aged 20–40 years in accordance with Davies and Shock [33]. Lastly, to describe the interdependence of fe on eGFR, a fit curve was calculated based on the ratio of the regression equations through the data points for renal plasma clearance (mL/min/kg) against eGFR (mL/min/1.73 m^2) and total plasma clearance (mL/min/kg) against eGFR. The increased non-renal clearance of milrinone at reduced renal function was attributed to its hepatic metabolism [31].

Lastly, to account for the effect of milrinone on cardiac index and consequently organ blood flow, a dose–response relationship was established. A literature search was carried out to identify studies that provided the necessary data to correlate milrinone's plasma concentration with dose and change in cardiac index. Studies were included if subjects were adult patients with reduced cardiac performance or healthy adult volunteers, milrinone was administered at different bolus doses ranging from 10 to 75 μg/kg over approximately 1 min, and milrinone plasma concentration and cardiac index values were measured at 5 min, at which time the effect is expected to reach maximum [27], except for one study, for which the first given values at 15 min were used to correlate plasma concentration and cardiac index. The two datasets were then analysed using the linear regression method; goodness of fit was assessed by determining adjusted R^2 and the significance (p-value)

Table 2 Results from ADMET Predictor™ linked with tissue expression site and substrate specificity for uridine diphosphate-glucuronosyltransferases

UGT	ADMET Predictor™		UGT description [30]		
	Qualitative probability of glucuronidation (Yes/No)	Classification accuracy (%)	Tissue expression site	Highest substrate specificity	Maximal specific activity (pmol/min/mg protein)
1A1	Yes	90	Liver, bile ducts, stomach, colon	Simple phenols/anthraquinones and flavones	1,900/1,720
1A3	No	94	Liver, bile ducts, stomach, colon	Coumarins/anthraquinones and flavones	1,970/1,072
1A4	Yes	94	Liver, bile ducts, colon	Primary/secondary amines	540/240
1A6	Yes	85	Liver, bile ducts, stomach, colon, brain	Simple/complex phenols	2,400/13,300
1A9	No	91	Liver, colon, kidney	Simple phenols/primary amines	5,300/1,800
1A10	Yes	93	Oesophagus, stomach, bile ducts, intestine, colon	Heterocyclic amines	156
2B7	Yes	92	Oesophagus, liver, intestine, colon, brain, kidney, pancreas	Opioids	3,462

UGT uridine diphosphate-glucuronosyltransferase

of the *F*-test. Finally, the dose–response relationship was established by substituting the predictive equation for plasma concentration into the equation for cardiac index change.

Based on this equation for cardiac index change, the bolus dose for milrinone with 50 μg/kg in accordance with the prescribing guidance would result in a cardiac index increase of 47 %. This increase is comparable with the reported cardiac index change of 49 % following a maintenance infusion dose of 0.5 μg/kg/min in patients with LCOS after cardiac surgery [34]. Considering the known (im-)precision for cardiac index determination [35, 36], a 47 % cardiac index increase was, therefore, adopted for therapeutic dosing of milrinone in the model. As a result of the cardiac index change, the increased blood flow was redistributed to the limbs [37, 38], heart [39], lungs [40] and brain [41] (Table 1).

Steps 1, 3, 5 and 6 in the workflow (Fig. 1) were followed to incorporate the drug model information into PK-Sim® without applying disease-model factors. Blood flow was manually altered in heart and brain to reflect the dose–response relationship of milrinone on cardiac index and the percentage of increased limb blood flow was equally assigned to skin and muscle [42]. Lung blood flow cannot be directly altered, but it must equate to the sum of all non-portal venous blood flows to maintain mass balance, leading to a 27 % change in lung blood flow, which was close to the expected literature value of 24 % for milrinone at 0.5 μg/min/kg [40]. Finally, organ distribution parameters for milrinone were generated using the tissue distribution model by Willmann et al. [43]. In all, the left-hand side of Fig. 2 visualises the final PBPK drug model to indicate the drug-dependent pharmacokinetic and pharmacodynamic components as well as the system components of the model.

2.1.2 *Disease Model*

Firstly, disease model parameter values were extracted from the literature and separately listed to reflect average age and sex, as well as the pre- and postoperative organ function in adult patients with and without LCOS after open heart surgery, as shown in Table 3. In the next step, the values were set in relation to the reference values in healthy adults aged 20–40 years; any deviations from these to adult patients aged 60–70 years were described as factorial changes in the disease model. The reference value for haematocrit was set to 47 % [44], plasma albumin to 3.5–5 g/dL [45] and cardiac index to 3.6 L/min/m^2 [46]. Organ blood flows were set to correspond to a factor of 1. The reference value for eGFR with 119 mL/min/1.73 m^2 was taken from Davies and Shock [33]; its comparison to the expected eGFR value in adults aged 60–70 years with 96 mL/min/1.73 m^2 and the preoperative value in patients without LCOS with 71 mL/min/1.73 m^2 allowed attribution of the overall factorial change of 0.6 to the normal age-related decline in eGFR (age factor 0.81) and impact due to disease (disease factor 0.74). Disease-related changes in active tubular secretion between healthy and diseased adults were quantified with the surrogate parameter kidney injury molecule 1 (KIM-1), which is a sensitive indicator of tubular damage. Similar to eGFR, the overall factorial changes were attributed to the normal age-related decline of tubular

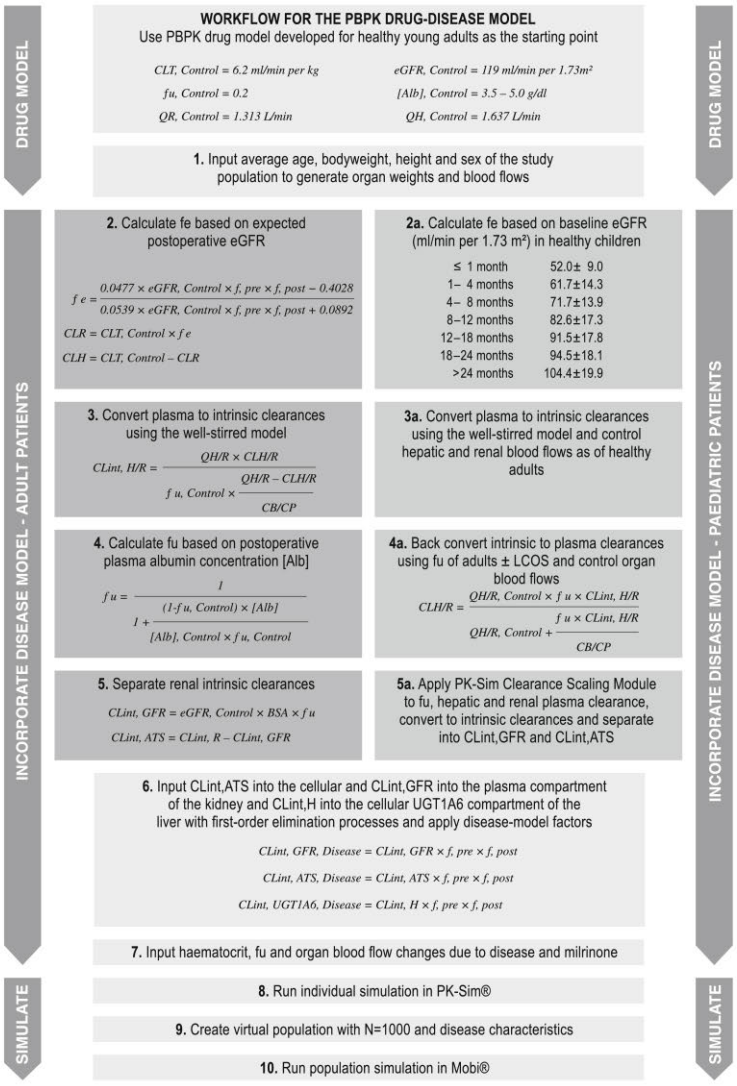

Fig. 1 Work flow for the physiology-based pharmacokinetic drug–model development. The workflow is subdivided into different steps: the physiology-based pharmacokinetic (PBPK) drug model developed for healthy young adults in accordance with the data by Stroshane et al. [26] is the base model for each simulation. The *light grey boxes* show common modelling pathways for adult and paediatric patients, and the *dark grey areas* point out differences in modelling. *[Alb]* plasma albumin concentration, *BSA* body surface area, *CB/CP* red blood cell-to-plasma concentration ratio and derived from PK-Sim® compartment predictions with the respective plasma fraction unbound, *CLH* hepatic plasma clearance of milrinone, *CLint,ATS* intrinsic clearance of milrinone due to active tubular secretion, *CLint,GFR* intrinsic clearance of milrinone due to glomerular filtration, *CLint,H/R* hepatic and renal intrinsic clearances of milrinone, *CLR* renal plasma clearance of milrinone, *CLT* total milrinone plasma clearance, *eGFR* estimated glomerular filtration rate, *fe* fraction of milrinone excreted unchanged in urine, *f, post* factor relating to postoperative organ functioning, *f, pre* factor relating to preoperative organ functioning, *fu* plasma fraction unbound, *QH* hepatic blood flow, *QR* renal blood flow

excretory capacity in accordance with Davies and Shock [33] (age factor 0.84) and impact due to disease (disease factor 0.76 in patients without LCOS). In contrast, glucuronidation is a process reported to be age independent [47, 48] and, therefore, the factorial change in UGT1A6 ultimately described the influence of disease. Lastly, the disease model and the drug model were combined according to the workflow in Fig. 1 to describe the altered pharmacokinetics of milrinone in adult patients with and without LCOS after open heart surgery.

2.1.3 *Drug–Disease Model Adaptation for Paediatric Patients*

The preoperative disease model factors defined for adult patients without LCOS were equally applied to paediatric

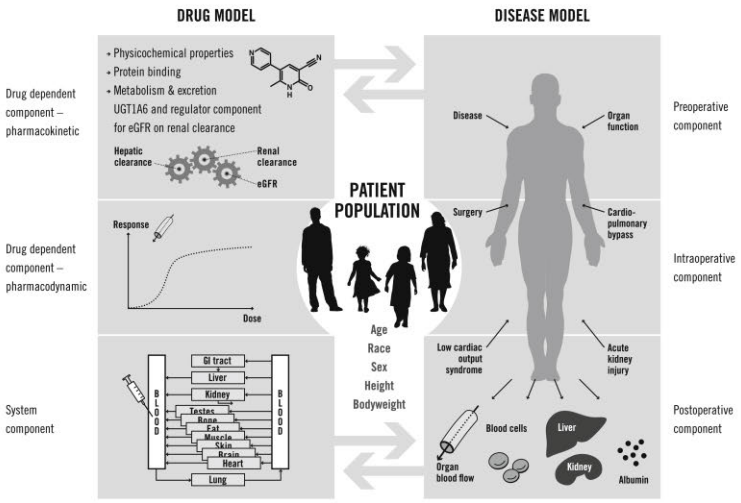

Fig. 2 Schematic presentation of the physiology-based pharmacokinetic (PBPK) drug–disease model for milrinone in adult and paediatric patients with open heart surgery. The figure shows the key elements of the PBPK drug–disease model: the PBPK drug model for milrinone, the disease model and the patient populations. The drug model, shown on the *left-hand side*, includes the drug-dependent components split into pharmacokinetics and pharmacodynamics, and the system component, which represents the whole-body PBPK modelling and simulation platform applied to the intravenous application of milrinone. The patient population, shown in the *middle*, is central to both the drug and disease model. Patient characteristics, such as age and race, are adjusted for in the drug model; pre- and postoperative organ functions are integrated in the disease model, shown on the *right-hand side*. The disease model includes the pre-, intra- and postoperative components associated with open heart surgery and considered important to describe the altered pharmacokinetics of milrinone in patients with and without low cardiac output syndrome after open heart surgery. Parameters with *inwards directed arrows* describe an influence on postoperative outcome parameters, which are used as input parameters for the disease model: organ blood flow, blood cells, liver and kidney function and albumin abundance. *eGFR* estimated glomerular filtration rate, *UGT1A6* uridine diphosphate-glucuronosyltransferase 1A6

patients with and without LCOS after correction for the normal age-related decline in renal function based on comparable disease-related changes. For example, Zappitelli et al. [49] showed that preoperative eGFR was reduced by a factor of 0.72 in paediatric patients with cardiac surgery when compared with healthy children of the same age, which is close to the factor found in adults as shown above. The study also showed that baseline eGFR was not significantly different between paediatric patients who did not develop acute kidney injury after cardiac surgery and those who did, which is indicative of LCOS. Comparable data were also available to quantify the impact of disease on active tubular secretion using KIM-1 [50–52]. In contrast to adult patients, kidney blood flow was also proportionally reduced in paediatric patients both with and without LCOS for model building based on research by Bernstein et al. [53] in experimental cyanotic heart disease. Due to the lack of information in the literature, the same interrelation was assumed for O-linked glucuronidation activity, and the factor for UGT1A6 defined for adult patients without LCOS was equally applied to paediatric patients with and without LCOS.

The postoperative disease model factors were assumed to be age independent and were, thus, equally applied to paediatric patients with and without LCOS, as previously done for adults. The same cardiac index reduction was also applied if not reported otherwise in the paediatric studies. However, haematocrit values for paediatric patients with and without LCOS were taken from Jonas et al. [54], who demonstrated that patients with lower intraoperative haematocrit (21.5 ± 2.9 %, mean ± SD) were more likely to have lower cardiac indexes in the first 24 h postoperatively and require more inotropic administration than patients with higher intraoperative haematocrit (27.8 ± 3.2 %). The 60-min off cardiopulmonary bypass values were used for model building, i.e. 33 ± 5 % and 35 ± 4.5 %, respectively. Lastly, plasma fraction unbound was scaled from the values in adult patients with and without LCOS to the paediatric age of interest using the model by McNamara and Alcorn [55], which is integrated in the PK-Sim®

PBPK Drug–Disease Model for Milrinone After Cardiac Surgery

Table 3 Quantitative description of pre- and postoperative organ functioning in adult patients undergoing open heart surgery

Parameter	Study description	Study results included in the disease model for patients without (−LCOS) and with LCOS (+LCOS) after open heart surgery/ comments	References
Part A: Preop characteristics			
Age, sex	Patients with CPB surgery ($N = 13,076$)	(−LCOS) 60.4 ± 13.1 years and 68 % male ($N = 11,287$, 86 %)	[103–110]
		(+LCOS) 65.7 ± 9.1 years and 61 % male ($N = 1,789$, 14 %)	
		Patients grouped into +LCOS were diagnosed with LCOS (need for postop IABP or inotropic support for more than 30 min in ICU) or in need of postop inotropic support due to low cardiac output, hypotension, inability to separate from CPB	
NYHA classification	Patients with CPB surgery ($N = 353$)	(−LCOS) Patients without postop HF after open heart surgery more likely to be in NYHA 1/2 than 3/4	[105]
		(+LCOS) Patients with postop HF after open heart surgery more likely to be in NYHA 3/4 than 1/2	
		Definition of postop HF: haemodynamic state secondary to pump failure	
Renal function			
GFR	Patients with CABG surgery ($N = 203$)	(−LCOS) Preop eGFR: 71 mL/min/1.73 m^2	[106]
		(+LCOS) Preop eGFR: 57 mL/min/1.73 m^2	
		Definition of LCOS: need for postop intra-aortic balloon pump or inotropic support for more than 30 min in ICU	
ATS	Patients with CHF and healthy controls ($N = 173$)	Healthy control: 551 ng/g UCr KIM-1	[111]
		(−LCOS) Patients with NYHA 1 and 2: 860 ng/g UCr KIM-1	
		(+LCOS) Patients with NYHA 3 and 4: 1,680 ng/g UCr KIM-1	
Liver function			
UGT1A6	Patients with CHF ($N = 12$)	(−LCOS) Patients aged 48 years with NYHA 2–4: 25 % reduction in paracetamol clearances	[112, 113]
	Rat model on right HF	(+LCOS) Metabolic glucuronide formation clearance of 4-nitrophenol reduced by 50 % under controlled blood flow and oxygenation	[114]
Organ blood flow			
Kidney	Patients with CHF ($N = 34$)	(+LCOS) Patients with CI > 2 L/min/m^2: renal fraction of cardiac output 11 %	[115]
Splanchnic, limbs	Patients with CHF	(−LCOS) Patients with NYHA 2: proportional blood flow reduction	[116]
		(+LCOS) Patients with NYHA 3 and 4: proportional blood flow reduction	
Skeletal muscle, kidney, heart, other	Data from human and animals with CHF	(−LCOS) Patients with mild to moderate CHF: proportional blood flow reduction to muscle, kidney, heart, brain and other	[117]
		(+LCOS) Patients with severe CHF: proportional blood flow reduction to muscle and other. Blood flow redistribution to heart and brain	
Part B: postop characteristics			
CI	Patients with elective cardiac surgery (CABG ± valve)	(−LCOS) Postop CI: 2.3 L/min/m^2 ($N = 29$)	[61]
		Study exclusion: need for inotropic drugs/IABP or CI ≥ 3 L/min/m^2	
		(+LCOS) Postop CI: 1.7 L/min/m^2 ($N = 120$)	[118]
		Definition of LCOS: CI < 2 L/min/m^2 and PCWP ≥ 10 mmHg	
HCT	Patients with CPB surgery ($N = 5,000$)	(−LCOS) Patients aged 63 years with preop HCT 40 %: postop HCT 25 % ± 1.9	[71]
		(+LCOS) Patients aged 67 years with preop HCT 33 %: postop HCT 20 % ± 3.4	
		Significant increase in LCOS incidence (use of IABP) in patients with postop HCT of 20 %	

Table 3 continued

Parameter	Study description	Study results included in the disease model for patients without (−LCOS) and with LCOS (+LCOS) after open heart surgery/ comments	References
Plasma albumin abundance	Patients with CPB surgery ($N = 19$)	(−LCOS) Patients with LVEF > 40 %: preop and postop (60 min post-CPB) plasma albumin levels 3.7 and 3.1 g/dL, respectively	[119]
		CI kept at ≥2.5 L/min/m^2 after CPB separation	
	Adult patients with CABG (off-pump)	(+ LCOS) Patients in the group with an albumin level <2.3 g/dL: preop and postop (day 0 and 1) plasma albumin were 3.6 and 2.3 g/dL, respectively	[120]
		Significant increase in LCOS incidence (use of inotropic drugs) in group with albumin levels <2.3 vs. >2.3 g/dL	
Renal function			
GFR	Patients with cardiac surgery ($N = 2{,}000$, 94 % on-pump)	(−LCOS) 72-h change in creatinine clearance (Cockroft-Gault) of 15 % vs. preop values on the day before surgery in approximately 75 % of the patients	[121]
		5 % of the patients were diagnosed with LCOS	
	Patients with cardiac surgery ($N = 1{,}307$, 90 % on-pump)	(+LCOS) 50 % increase in creatinine over baseline (baseline creatinine 1.5–3 mg/dL) or above 2 mg/dL (baseline creatinine <1.5 mg/dL)	[122, 123]
		Equals definition for acute kidney injury in the studies. 62–100 % of the patients with acute kidney injury were diagnosed with LCOS	
ATS	Rat model with experimental renal failure	(−LCOS) ATS clearance reduced by 35 % by salicylate (GFR reduction 12 %)	[124]
		(+LCOS) ATS clearance reduced by 57 % by gentamicin (GFR reduction 53 %)	
		Clearance due to ATS determined with exogenous N-methylnicotinamide	
Liver function			
UGT1A6	Patients with liver transplant	(−LCOS) Paracetamol glucuronide urinary recovery 22 % lower on day 2 vs. day 180 postop	[125]
	Primary rat hepatocytes	(+LCOS) Paracetamol glucuronide clearance reduced by 36 % during prolonged moderate hypoxia	[126]
Organ blood flow			
Splanchnic	Patients with cardiac surgery ($N = 16$)	(−LCOS) Proportional blood flow reduction in patients with CI >1.75 L/min/m^2	[127]
	Porcine model of cardiogenic shock	(+LCOS) Disproportional reduction (factor 0.6) in hepatic artery, portal vein and celiac artery blood flow; associated CI reduction 50 %	[128]
Skin, bone, fat, kidney	Dog model of HF	(−LCOS) Proportional blood flow reduction (CI reduction 41 %)	[129]
		(+LCOS) Proportional blood flow reduction (CI reduction 54 %)	
Muscle	Dog model of HF	(−LCOS) Proportional blood flow reduction (CI reduction 42 %)	[129, 130]
		(+LCOS) Disproportional blood flow reduction (factor 0.6, CI reduction 54 %)	
Brain, heart	Rat model of haemorrhage	(+LCOS) Blood flow redistribution, increased flow to brain (2/3) and heart (1/3, CI reduction 50 %)	[131]

ATS active tubular secretion, *CABG* coronary artery bypass grafting, *CHF* chronic heart failure, *CI* cardiac index, *CPB* cardiopulmonary bypass, *(e)GFR* (estimated) glomerular filtration rate, *HCT* haematocrit, *HF* heart failure, *IABP* intraaortic balloon pump, *ICU* intensive care unit, *KIM-1* kidney injury molecule-1, *LCOS* low cardiac output syndrome, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *PCWP* pulmonary capillary wedge pressure, *postop* postoperative, *preop* preoperative, *UCr* Urinary creatinine, *UGT1A6* uridine diphosphate-glucuronosyltransferase 1A6

Clearance Scaling Module [19]. McNamara and Alcorn relate the ratio of the plasma albumin concentration between infants and adults to the plasma fraction unbound in adults to predict the plasma fraction unbound for infants. Apart from that, it was assumed that paediatric patients show the same dose–response relationship of milrinone on blood flow as adults do. This was based on research by Chang et al. [56], who reported a cardiac index increase of 42 ± 22 % (mean ± SD) following a milrinone loading dose of 50 μg/kg in neonates with LCOS after cardiac surgery and a cardiac index increase of 47 ± 14 % following a maintenance infusion of 0.5 μg/kg/min. Due to the lack of urinary excretion data for milrinone at a young age, fractional renal plasma clearance of milrinone was assumed to depend on eGFR in paediatric patients as it is in adults.

In accordance with Edginton et al. [19] and Björkman [21], the hepatic and renal plasma clearance of milrinone were "retrogradely" scaled from the corresponding values in healthy adults to the paediatric age of interest using the PK-Sim® Clearance Scaling Module. Thus, scaling of renal clearance was based on the exponential maturation models for glomerular filtration rate (GFR) and active tubular secretion by Hayton [57]; scaling of hepatic clearance via UGT1A6 was based on the age-dependent paracetamol glucuronide to sulphate ratio in children [58]. The disease model factors were applied afterwards as shown in Fig. 1.

2.1.4 Drug–Disease Model Evaluation

In total, nine different studies (see the Online Resource: Supplementary table 1) were used to assess the predictive performance of the PBPK drug–disease model for healthy adults [26, 59], adult patients [60–64] and paediatric patients after open heart surgery [7–9], which included the model building dataset for the PBPK drug model. The dataset of one paediatric study [7] investigating the efficacy of milrinone for LCOS prevention was split into patients with and without LCOS based on the sampling schedule. This way, patients with only one plasma sample or a sample taken after 480 min but before study end were likely to have developed LCOS in the course of the study. Thus, the split dataset was used to evaluate the model for paediatric patients both with and without LCOS after surgery. In addition, the study by Benotti and Hood [65] in adult patients not undergoing surgery but with comparable age, sex and physiological functioning to adult patients with LCOS after surgery was used to externally evaluate the accurateness of the preoperative model factors for organ blood flows, hepatic and renal function. However, the input parameter values for haematocrit of 38 % [66] and plasma fraction unbound of 20 % [67] were chosen to be reflective of heart failure patients without surgery.

Populations of 1,000 virtual individuals were created to be representative of the patient cohorts in the evaluation studies using the PK-Sim® Population Module, which links age, sex, height, bodyweight and ethnicity dependence of mean values and variability to relevant anatomical parameters, such as blood flow values, based on in-built adult and paediatric reference databases for Europeans, Asians and White Americans [24]. Height and bodyweight for adult patients were supplemented with the reference values from the National Health and Nutrition Examination Survey (NHANES) III [68] if not provided in the original study. For paediatric patients, height or body surface area that corresponded with the same percentile as bodyweight for age and sex were based on the World Health Organization's growth standards for children [69, 70]. A female sex participation rate of 43 % was assumed if no further information was provided in the paediatric studies and based on the large clinical trial by Hoffman et al. [12] with 227 paediatric cardiac patients.

In addition to the interindividual variability of physiological parameters predefined by the population module, variability for the hepatic and renal clearance pathways was based on the total plasma clearance of milrinone with a logarithmic SD (log SD) of 1.6 [61, 62] and haematocrit in accordance with Habib et al. [71] for adult patients with and without LCOS with SDs of 3.4 and 1.9 %, respectively. In those with heart failure not undergoing surgery, variability for organ clearance (log SD 1.4) and haematocrit (SD 7 %) were derived from Woolfrey et al. [31] and Androne et al. [66], respectively. Lastly, a uniform variability of ±10 % was set around plasma fraction unbound to account for the reported range in the literature [11]. Except for haematocrit, for which the study results by Jonas et al. [54] were adopted, the variabilities for clearance and plasma fraction unbound in paediatric patients were set to be in accordance with adult patients undergoing surgery [72, 73]. Apart from considering population variability for execution of the simulations, arterial plasma sampling was assumed for patients with surgery and peripheral venous plasma sampling for healthy adults and patients without surgery if no information was provided in the studies. The population simulations were executed in Mobi® (version 2.3, Bayer Technology Services, Leverkusen, Germany), which is completely integrated with PK-Sim®.

To assess the accuracy of prediction, the mean relative deviation (MRD) and the average fold error (AFE) were calculated for the predicted geometric mean (PRED) and observed (OBS) plasma concentrations as measure of precision and bias using Eqs. 1 and 2, respectively [19, 74]. The decision to use these figures of merits was based on the log-normal distribution of absolute errors between OBS and PRED.

$$\mathrm{MRD} = 10^{\sqrt{1/N \sum_{i=1}^{N} \left(\log \frac{\mathrm{PRED}}{\mathrm{OBS}}\right)^2}} \quad (1)$$

$$\mathrm{AFE} = 10^{\left|1/N \sum_{i=1}^{N} \log \frac{\mathrm{PRED}}{\mathrm{OBS}}\right|} \quad (2)$$

A model prediction with AFE and MRD ≤2 was considered successful, meaning that the predictions were on average equal or less than twofold off [19, 74]. For the observed data, original plasma concentration–time profiles were provided by the authors or the marketing authorisation holder for three adult studies [26, 61, 64] and for two paediatric studies [7, 8]. For all other studies, the profiles were digitised from published plots using ScanData (Bayer Technology Services, Leverkusen, Germany). Detailed information on the observed plasma concentration data is provided in the Online Resource (Supplementary table 2). Goodness-of-fit plots were used for the graphical evaluation and the percentage coverage of observed plasma concentration within the 90 % prediction interval calculated. The prediction accuracy of total plasma clearance and terminal volume of distribution were assessed with the fold-error (FE) using Eq. 3, for which a value ≤2 was also considered successful [75].

$$\mathrm{FE} = \begin{cases} \dfrac{\mathrm{PRED}}{\mathrm{OBS}}, & \text{if PRED} > \text{OBS} \\ \dfrac{\mathrm{OBS}}{\mathrm{PRED}}, & \text{if OBS} > \text{PRED} \end{cases} \quad (3)$$

Predicted total plasma clearance and terminal volume of distribution were derived by non-compartmental analysis using Matlab™ (version 7.12, The MathWorks Inc., Natick, MA, USA). If not provided in the publications, the observed comparative values were also derived by non-compartmental analysis using PKSolver [25], for which the observed plasma concentrations following different doses of milrinone were dose-normalised to 50 μg/kg, 0.45 μg/kg/min, 50 μg/kg, 50 μg/kg and 0.5 μg/kg/min for the studies by Stroshane et al. [26], Benotti and Hood [65], Butterworth et al. [61] and Bailey et al. [7], respectively. The performance of the PBPK drug–disease model in terms of the median prediction error was compared with results obtained by Bailey et al., in which a 3-compartment model using non-linear mixed–effect modelling (NONMEM) techniques [8] and a weight-normalised one-compartment NONMEM model [7] was used for the prediction of milrinone pharmacokinetics. Furthermore, the coefficients of variations were determined for the total plasma clearance and volume of distribution and compared with results by Bailey et al. [7] for paediatric patients without LCOS aged 0–1 month and 1–24 months.

A parametric sensitivity analysis was conducted using the in-built analysis tool in Mobi® to identify and rank parameters that were most critical for the model output defined as plasma concentration at steady state. For this, population simulations with 1,000 virtual individuals were run that were representative of the different disease states and ages using the models for Butterworth et al. [61], Das et al. [62], Bailey et al. [8] and Ramamoorthy et al. [9]; dosing was unified to a maintenance infusion of 0.5 μg/kg/min over 24 h and model output was assessed at 24 h. The plausible range of model parameter variation was based on the values of the virtual individuals. The sensitivity coefficients were normalised so that the fractional change in model output was set in relation to the fractional change in model input. A model was considered robust if all normalised sensitivity coefficients had values ≤1 in accordance with Clewell and Andersen [76].

2.2 Applications of the PBPK Drug–Disease Model

After successful evaluation of model performance, the PBPK drug–disease model was applied to simulate milrinone exposure in paediatric patients for LCOS treatment in accordance with the SmPC [11] and for LCOS prevention in accordance with the PRIMACORP (PRophylactic Intravenous use of Milrinone After Cardiac OpeRation in Pediatrics) trial [12] as well as current hospital practices as identified by EuLoCOS-Paed [4, 5], a recent European-wide survey on the treatment and prevention for LCOS in paediatric patients with open heart surgery.

In this respect, dosing was simulated for LCOS treatment and prevention, for which the model characteristics for patients with and without LCOS were adopted, respectively. Generic paediatric patient populations of different ages were created each of 1,000 virtual individuals and the level of chronic malnutrition associated with congenital heart disease was taken into account [77]. Thus, bodyweight and height was chosen to represent a distribution with the 50 % percentile as median (approximately 0 % malnutrition) in neonates, the 15 % percentile for bodyweight and height (79–84 % malnutrition) in infants and children 29 days up to 3 years, and the 25 % percentile for bodyweight and height (58–61 % malnutrition) in children and adolescents 3–15 years.

Drug exposure was evaluated to comprise 90 % of the virtual patient population within the therapeutic target range of milrinone of 100–300 ng/mL in plasma [6]. If current dosing led to a significant proportion of patients (≥25 %) being under- or overdosed, alternative dosing regimens were evaluated with the aim of avoiding underdosing and to minimise overdosing. For the loading dose in particular, overshooting plasma concentrations and the

asscociated risk of hypotension [78, 79] and a drop below 100 ng/mL after decline from the peak concentration and before reaching steady state should be avoided; peak plasma concentrations should also be comparable with the final steady-state concentrations.

The steps were repeated for adult patients to assess the applicability of bodyweight-based dose scaling from adult to paediatric patients. Dosing for LCOS treatment was extracted from the SmPC for milrinone [11] and for LCOS prevention from clinical trials [60]. Generic adult patient populations were reflective of age and sex in accordance with Table 3; height and bodyweight were supplemented from NHANES III [68].

3 Results

3.1 Development of the PBPK Drug–Disease Model

3.1.1 Drug Model

Development steps towards a PBPK drug model for milrinone involved the quantitative description of the influence of renal impairment on fractional renal clearance and a dose–response relationship of milrinone on cardiac index. The former was given by the analysis of renal and total plasma clearance data of milrinone in healthy young adults and adult patients with renal impairment, for which fe was used as a marker of the renal contribution to total plasma clearances depending on eGFR (Fig. 3). Based on the ratio of the resultant linear regressions between milrinone's renal plasma clearance against eGFR (renal clearance $= 0.0477 \times \text{eGFR} - 0.4028$; adjusted $R^2 = 0.943$, $p < 0.001$) and between milrinone's total plasma clearance and eGFR (total clearance $= 0.0539 \times \text{eGFR} + 0.0892$; adjusted $R^2 = 0.915$, $p < 0.001$), the interdependence of fe on eGFR was described with Eq. 4:

$$\text{fe} = \frac{0.0477 \times \text{eGFR} - 0.4028}{0.0539 \times \text{eGFR} + 0.0892} \quad (4)$$

The dose–response relationship of milrinone with regard to percentage change in cardiac index was given by Eq. 5, which was based on the results of the linear regression through the origin between milrinone's plasma concentration and dose (plasma concentration $= 5.133 \times$ bolus dose; adjusted $R^2 = 0.983$, $p < 0.001$) using three studies [26, 61, 80] with 63 subjects and the linear regression between percentage change in cardiac index and milrinone's plasma concentration (Δ cardiac index $[\%] = 0.105 \times$ plasma concentration $+ 19.627$; adjusted $R^2 = 0.528$, $p = 0.001$) using four studies [60, 61, 80, 81] with 71 subjects.

$$\Delta \text{ Cardiac index } [\%] = 0.539 \times \text{Bolus dose} + 19.627 \quad (5)$$

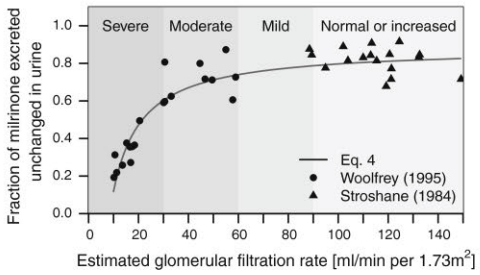

Fig. 3 Correlation between the fraction of milrinone excreted unchanged in urine and estimated glomerular filtration rate. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guideline on chronic kidney disease [32] was used to relate the fraction of milrinone excreted unchanged in urine to kidney function expressed as estimated glomerular filtration rate. The plot visualises the effect of normal or increased, mildly, moderately and severely reduced glomerular filtration rate on the renal metabolism of milrinone, which can be quantified with Eq. 4. Data from Stroshane et al. [26] and Woolfrey et al. [31] were used to establish to intercorrelation

3.1.2 Disease Model

Factorial changes of the key parameters cardiac index, haematocrit, plasma albumin abundance, various organ blood flows, UGT1A6, and active tubular secretion activity and GFR in patients with open heart surgery from the respective reference values in healthy adults made up the disease model (Table 4). The disease model was combined with the drug model and a schematic presentation of the final PBPK drug–disease model is shown in Fig. 2.

3.2 Evaluation of the PBPK Drug–Disease Model

The numerical evaluation of the PBPK drug–disease model showed that the simulated plasma concentration curves accurately matched the experimental observations in healthy adults, adult patients with and without LCOS, and paediatric patients without LCOS (Table 5). Bias was low throughout (AFE 1.1 ± 0.1, mean $\pm$ SD) and precision acceptable with all MRDs were less than 2 but reflective of the variability in the pharmacokinetic datasets. In addition, predicted total plasma clearances and terminal volumes of distribution were similar to literature values, with an average deviation of 24 % for volume of distribution. Model prediction accuracy was lowest for paediatric patients with LCOS but within the acceptable limits (MRDs 1.60–1.97) and there was a good match between predicted total plasma clearance, volume of distribution and plasma concentrations at steady state for paediatric

Table 4 Physiological parameter changes associated with pre- and postoperative organ function in adult patients with open heart surgery

Parameter	Patients without LCOS		Patients with LCOS	
	Factor pre-surgery	Factor post-surgery	Factor pre-surgery	Factor post-surgery
Cardiac index	–	0.64	–	0.47
Haematocrit	–	0.53	–	0.42
Plasma albumin	–	0.84	–	0.64
Blood flows				
Kidney	–	0.64	0.58	0.47
Splanchnic	–	0.64	–	0.28
Muscle	–	0.64	–	0.28
Heart[a]	–	0.64	–	0.47
Brain[a]	–	0.64	–	0.47
Other organs[b]	–	0.64	–	0.47
Renal function				
GFR	0.60	0.85	0.48	0.5
ATS	0.64	0.65	0.33	0.43
Liver function				
UGT1A6	0.75	0.78	0.5	0.64

Parameter differences between healthy young adults and patients with and without LCOS after open heart surgery are presented as factorial changes and separated into the effects due to baseline disease (factor pre-surgery) and open heart surgery (factor post-surgery). The respective parameter values in healthy adults were set to be 100 %

ATS active tubular secretion, *GFR* glomerular filtration rate, *LCOS* low cardiac output syndrome, *UGT1A6* uridine diphosphate-glucuronosyltransferase 1A6, – factor not applied to physiology-based pharmacokinetic drug–disease model

[a] In addition, blood flows from organs with a disproportional reduction were redistributed to brain (2/3) and heart (1/3)

[b] Lung blood flow could not be directly altered; it was the result of the sum of all non-portal venous blood flows to maintain mass balance

patients with LCOS and the observed values by Ramamoorthy et al. [9].

The graphical evaluation also indicated that the drug–disease model adequately represented the population variability for the different patient groups and disease states (Fig. 4). A set of overpredicted plasma concentrations was, however, noticeable for paediatric patients without LCOS on the right-hand side of Fig. 4; in addition, the relative deviation from the line of identity increased with higher plasma concentrations. In all, 82 and 80 % of the observed plasma concentrations were within the 5th and 95th prediction interval for adult patients without and with LCOS, respectively. For paediatric patients without and with LCOS, 86 and 70 % of the observed plasma concentrations were within the prediction interval, respectively.

As a further verification of the PBPK drug–disease model, the preoperative parameter values of adult patients with LCOS after surgery were externally evaluated in patients not undergoing surgery but with comparable age, sex and physiological functioning. The results demonstrated accurate predictive performance, as shown in Table 5 and Fig. 4, and supported the validity of the model.

The direct comparison of the median prediction errors for milrinone plasma concentrations in the two studies by Bailey et al. for paediatric patients without LCOS demonstrated an improvement by 6 and 13 % using the PBPK drug–disease model. Specifically, the median prediction error for the three-compartment model [8] was reported to be 25 versus 19 % for the PBPK model; the median prediction error for the weight-normalised one-compartment model [7] was reported to be 39 versus 26 % for the PBPK model. Furthermore, prediction variability for milrinone clearance and volume of distribution was improved by up to 120 % for paediatric patients without LCOS in the age groups 0–1 month and 1–24 months using the PBPK drug–disease model (Table 5) compared with Bailey et al. [7]. In that study, the coefficients of variation for milrinone plasma clearance were reported to be 157 and 57 % for neonates and infants aged 1–24 months, respectively; the coefficients of variation for volume of distributions were reported to be 38 and 85 % for the same respective age groups.

Model sensitivity analysis showed that depending on the age and disease state analysed, only four to seven out of 221 organism, compound, application and species parameters explained 90 % of the variability of the plasma concentrations at steady state, of which kidney blood flow, haematocrit and the intrinsic clearances due to active tubular secretion and UGT1A6 were important for adult and paediatric patients (Fig. 4). In contrast, plasma

PBPK Drug–Disease Model for Milrinone After Cardiac Surgery

Table 5 Numerical evaluation of the predictive performance of the physiology-based pharmacokinetic drug–disease model

Subjects/study	Bias	Precision	Total plasma clearance (mL/min/kg)			Terminal volume of distribution (mL/kg)		
			Observed (mean ± SD)	Predicted (mean ± SD)	FE	Observed (mean ± SD)	Predicted (mean ± SD)	FE
Healthy adults								
Stroshane et al. [26]	1.01	1.39	6.3 ± 1.3	6.4 ± 1.8	1.02	462 ± 163	503 ± 145	1.09
Tsunoo et al. [59]	1.05	1.11	5.9 ± 0.3	6.4 ± 1.6	1.08	372[a]	406 ± 100	1.09
Adult patients with heart failure								
Benotti and Hood [65]	1.17	1.78	2.6 ± 1.0	2.9 ± 0.6	1.12	468 ± 147	441 ± 30	1.06
Adult patients without LCOS								
Butterworth et al. [61]	1.12	1.69	4.5 ± 1.8	5.1 ± 2.0	1.13	495 ± 161	617 ± 183	1.25
Bailey et al. [60]	1.11	1.34	3.9 ± 0.7	4.4 ± 1.4	1.13	438 ± 116	536 ± 139	1.22
Adult patients with LCOS								
Das et al. [62]	1.03	1.45	2.2 ± 0.7	2.1 ± 0.7	1.05	310 ± 129	514 ± 100	1.66
De Heert et al. [63] (low dose)	1.08	1.16	2.4 ± 1.5	2.3 ± 0.7	1.04	436[a]	529 ± 105	1.21
De Heert et al. [63] (high dose)	1.03	1.07	2.1 ± 0.7	2.3 ± 0.7	1.10	467[a]	532 ± 106	1.14
Hasei et al. [64]	1.05	1.53	2.6 ± 1.1	2.3 ± 0.7	1.13	NA	513 ± 104	NA
Paediatric patients without LCOS								
Bailey et al. [8] (bolus)	1.06	1.69	4.2 ± 1.9	5.0 ± 2.2	1.19	697 ± 143	551 ± 135	1.26
Bailey et al. [8] (bolus + infusion)	1.05	1.42	5.9 ± 1.3	6.0 ± 2.5	1.02	NA	598 ± 159	NA
Bailey et al. [7] (0–1 months)	1.12	1.71	NA	3.0 ± 1.1	NA	NA	510 ± 66	NA
Bailey et al. [7] (1–24 months)	1.10	1.76	NA	4.7 ± 1.6	NA	NA	589 ± 104	NA
Bailey et al. [7] (2–8 years)	1.00	1.21	NA	6.0 ± 2.0	NA	NA	583 ± 157	NA
Paediatric patients with LCOS								
Ramamoorthy et al. [9] (0–12 years)	NA	NA	4.5 ± 1.8	4.9 ± 2.4	1.09	830 ± 400	647 ± 142	1.28
Ramamoorthy et al. [9] (0–1 years)	NA	NA	3.8 ± 1.0	3.7 ± 1.3	1.03	900 ± 400	577 ± 99	1.56
Ramamoorthy et al. [9] (1–12 years)	NA	NA	5.9 ± 2.0	4.4 ± 2.0	1.34	700 ± 200	635 ± 154	1.10
Bailey et al. [7] (0–1 months)	1.41	1.97	NA	2.2 ± 0.8	NA	NA	546 ± 63	NA
Bailey et al. [7] (1–24 months)	1.00	1.74	NA	3.6 ± 1.2	NA	NA	622 ± 94	NA
Bailey et al. [7] (2–8 years)	1.35	1.60	NA	4.7 ± 1.5	NA	NA	641 ± 146	NA
Mean ± SD	1.10 ± 0.12	1.51 ± 0.27			1.11 ± 0.08			1.24 ± 0.19

Data presentation: bias and precision were calculated as average fold error and mean relative deviation based on the observed plasma concentrations and predicted geometric mean plasma concentrations

FE fold-error, *LCOS* low cardiac output syndrome, *NA* not available, *SD* standard deviation

[a] Calculated as the quotient of clearance and terminal elimination rate constant provided in the publication

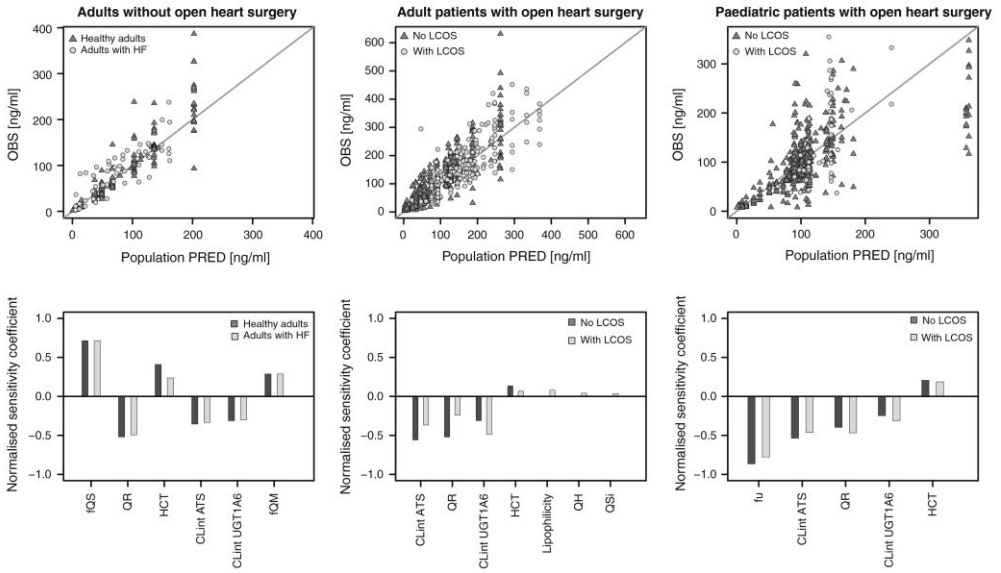

Fig. 4 Graphical evaluation of the predictive performance of the physiology-based pharmacokinetic drug–disease model. The *upper panel* shows the observed-versus-predicted plots for the plasma concentrations of milrinone for adults not undergoing open heart surgery, namely healthy young adults and adult patients with heart failure, adult patients with and without LCOS after surgery, and paediatric patients with and without LCOS after surgery. The *line of identity* is shown in each plot. The *lower panel* shows the results from the parametric sensitivity analysis of the respective physiology-based pharmacokinetic models. Depending on the evaluated case, four to seven out of 221 organism, compound, application and species parameters explained 90 % of the variability of the model output, which was defined to be the plasma concentration at steady state. *CLint,ATS* intrinsic clearance due to active tubular secretion, *CLint,UGT1A6* intrinsic clearance due to hepatic uridine diphosphate-glucuronosyltransferase 1A6, *fQM* fraction of peripheral blood flow in muscle, *fQS* fraction of peripheral blood flow in skin, *fu* plasma fraction unbound, *HCT* haematocrit, *HF* heart failure, *LCOS* low cardiac output syndrome, *OBS* observed plasma concentrations, *Population PRED* population-predicted plasma concentration, *QH* liver blood flow, *QR* kidney blood flow, *QSi* small intestine blood flow

concentration at steady state was sensitive to changes in plasma fraction unbound in paediatric patients but not in adult patients. Overall, normalised maximum sensitivity coefficients ranged from −0.84 to 0.71, which demonstrated that the changes in model input parameters were not amplified in the model output and indicated model robustness. Thus, the model provided the means to evaluate current milrinone prescribing for LCOS treatment and prevention in adult and paediatric patients after open heart surgery.

3.3 Applications of the PBPK Drug–Disease Model

Simulating a fixed, bodyweight-normalised dosing regimen for milrinone in paediatric patients of different age groups showed a non-linear dependence of milrinone's steady-state plasma concentration on age (Fig. 5). Consequently, current prescribing for LCOS prevention, which is based on fixed dosing regimens, resulted in supra- and subtherapeutic plasma concentrations for most paediatric patients. Dosing in accordance with the PRIMACORP study results [12], i.e. milrinone loading with 75 μg/kg over 60 min followed by a maintenance infusion of 0.75 μg/kg/min, provided adequate exposure only for patients aged 0.5–1 year and 9–15 years following the maintenance infusion, whereas the loading dose resulted in low-range therapeutic plasma concentrations for all patients older than 1 month. In contrast, the actually practiced dosing across Europe as described in EuLoCOS-Paed [4], i.e. a milrinone maintenance infusion of 0.5 μg/kg/min without loading, provided adequate drug exposure only for neonates older than 24 h, for which it took around 2 h to reach therapeutic plasma concentrations.

In contrast to LCOS prevention, the maintenance infusion dose for paediatric LCOS treatment in the SmPC ranges from 0.25 to 0.75 μg/kg/min. This threefold dose range allowed prediction of adequate steady-state plasma concentrations of milrinone for paediatric patients if

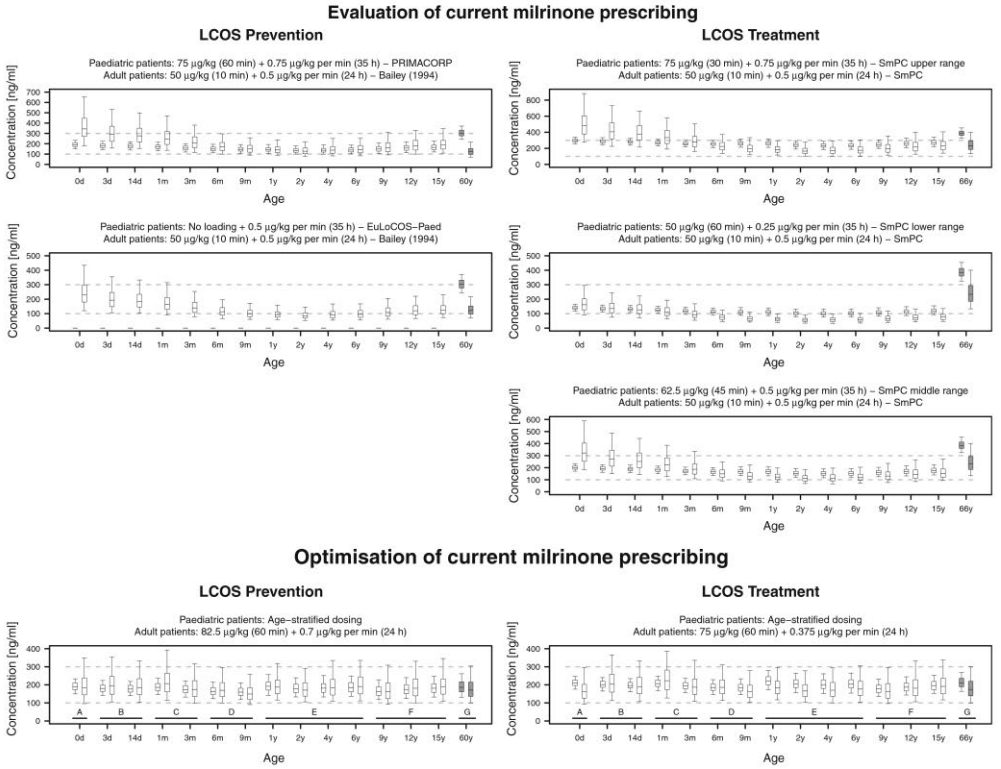

Fig. 5 Evaluation and optimisation of current milrinone prescribing for the treatment and prevention of LCOS in paediatric and adult patients after open heart surgery. Each plot for LCOS prevention and treatment contains a separate box plot for the loading (*left-side*) and maintenance infusion dose (*right-side*) for 14 ascending paediatric age groups (*white box plots*) and the adult population (*grey-shaded box plots*). One dosing regimen evaluated for LCOS prevention did not include a loading dose and is marked with a horizontal line at zero for each paediatric age group. The lettering of the age clusters in the "Optimisation of current milrinone prescribing" graphs and the corresponding dosing regimens are explained in detail in Table 6. For the box plot, the *horizontal line* represents the geometric mean of the population, the *box* includes the 25th and 75th percentile, the *error bars* (*whiskers*) include the 5th and 95th percentile. The dosing regimens used for the evaluation of current milrinone prescribing were extracted from the PRIMACORP trial [12], the study by Bailey et al. [60], the EuLoCOS-Paed survey [4] and the milrinone SmPC [11]. *LCOS* low cardiac output syndrome, *SmPC* summary of product characteristics

applied in an age-dependent manner (Fig. 5). However, this was only true if applied in an age-dependent manner, for which no guidance exists. Therefore, "blind" dosing resulted in supratherapeutic levels for patients aged less than 3 months using the upper dose range of milrinone and in subtherapeutic levels for patients beyond the neonatal period, i.e. first 24 h of life, using the lower dose range of milrinone. The comparison with LCOS prevention also demonstrated that the same maintenance infusion of 0.5 µg/kg/min resulted in 1.4-fold higher drug exposure for paediatric patients with LCOS.

Consequently, optimised dosing strategies were developed for LCOS treatment and prevention in paediatric patients with open heart surgery that considered the age-dependent and pathophysiological differences (Table 6; Fig. 5). Six clusters with age groups of comparable exposure following a given dose of milrinone were formed. The lowest dose was predicted for the newborn period (A) and the highest dose for patients aged 1–9 years (E). Patients being 9–15 years old (F) were predicted to require the same dose as did patients being 1–6 months old (C) in order to achieve the therapeutic target range for milrinone.

Table 6 Optimised milrinone dosing regimens for low cardiac output syndrome treatment and prevention

	Group[a]	LCOS prevention		LCOS treatment	
		Loading (μg/kg over 60 min)	Maintenance (μg/kg/min)	Loading (μg/kg over 60 min)	Maintenance (μg/kg/min)
Paediatric patients					
0 days	A	75	0.4	75	0.25
>0 days to <1 month	B	75	0.5	75	0.375
1 to <6 months	C	82.5	0.625	82.5	0.5
6 months to <1 year	D	82.5	0.75	82.5	0.625
1 to <9 years	E	100	1.0	100	0.75
9 to 15 years	F	82.5	0.75	82.5	0.625
Adult patients	G	82.5	0.7	75	0.375

LCOS low cardiac output syndrome

[a] Group refers to Fig. 5 "Optimisation of current milrinone prescribing"

In addition, a loading dose administered over 60 min was predicted to provide optimal results; the loading dose for a specific cluster did not differ between LCOS treatment and LCOS prevention but among the clusters themselves. Lastly, optimised dosing for LCOS treatment was lower than for LCOS prevention.

In adult patients, simulating current dosing for LCOS prevention and treatment demonstrated exposure differences of a factor of 1.9 between patients with and without LCOS following a maintenance infusion of 0.5 μg/kg/min (Fig. 5). Supratherapeutic plasma levels of milrinone were predicted for both patient groups following a loading of 50 μg/kg over 10 min; around 25 % of the patients with and without LCOS were predicted to have supra- and subtherapeutic steady-state plasma concentrations, respectively (Fig. 5). Consequently, optimised dosing strategies were also developed for adult patients, resulting in loading doses given over 60 min and maintenance infusion doses that were around 25 % lower and higher for LCOS treatment and prevention than current dosing, respectively (Fig. 5; Table 6). More importantly, optimised dosing strategies for the loading and maintenance infusion of milrinone differed between adult and paediatric patients.

4 Discussion

The study describes the potential of PBPK drug–disease modelling for paediatric patients applied to the case of milrinone for LCOS treatment and prevention after open heart surgery and indicates that current prescribing is suboptimal towards achieving the therapeutic target range of milrinone across all paediatric age groups (Fig. 5). Consequently, optimised milrinone dosing strategies for paediatric patients are presented based on the findings from the PBPK drug–disease model: milrinone dosing is age stratified and differs not only between LCOS treatment and prevention but also between paediatric and adult patients (Fig. 5; Table 6).

A system–biology-based approach was chosen in this study to complement the existing knowledge on the pharmacokinetics of milrinone in paediatric patients established by non-linear mixed–effect models [7, 8], which described a linear age dependency of milrinone's total plasma clearance but failed to predict plasma concentration in a recent practice evaluation [10]. In contrast, the present study identified a non-linear change in steady-state plasma concentration and, therefore, clearance of milrinone with age. The non-linear change in milrinone clearance with age reflects the bodyweight-normalised GFR versus age profile for neonates, infants, children and adolescents in accordance with the kidney maturation and growth model described by Hayton [57]. This is expected given the strong linear correlation between GFR and total plasma clearance as derived for Eq. 4. A similar elimination profile has also been demonstrated for levofloxacin, a drug with comparable plasma protein binding and renal elimination characteristics [82], using PBPK modelling [19] and an allometric model for bodyweight and age [83]. This confirms the necessity to consider growth and maturation of organ function during model building to adequately describe the pharmacokinetics of milrinone across the entire paediatric age range.

In addition to organ growth and maturation, the system–biology approach allowed the inclusion of pathophysiological parameter changes in the PBPK model based on the available knowledge on pre- and postoperative organ function in adult and paediatric patients with and without LCOS after open heart surgery. These parameter changes were summarised in a disease model, which was independent of the PBPK drug model for milrinone (Table 4). Their combination into a combined PBPK drug–disease model enabled the accurate description of existing

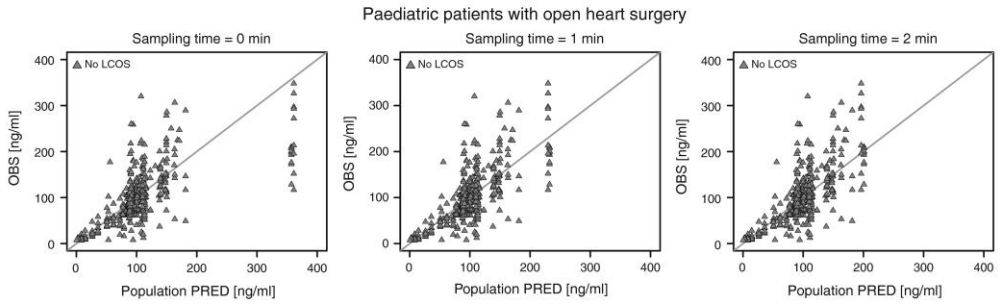

Fig. 6 Goodness-of-fit plots for the prediction of plasma concentrations from paediatric patients without LCOS for different sampling times. The plots visualise the improved prediction accuracy if the initial sampling time for milrinone plasma concentrations is changed from 0 min to 1 and 2 min in the study by Bailey et al. [8] with paediatric patients without LCOS. *LCOS* low cardiac output syndrome, *OBS* observed plasma concentrations, *Population PRED* population-predicted plasma concentration

pharmacokinetic studies of milrinone in patients (Table 5; Fig. 4). A deviation, however, was detected for the prediction of the plasma concentrations for paediatric patients without LCOS as shown in Fig. 4, mainly due to an overprediction of the initial plasma concentrations from the study by Bailey et al. [8]. This is likely to be based on reporting bias in the original study, which only stated that arterial samples were drawn immediately after the loading dose was complete but without specifying the exact time. Given this limited information on sampling, the prediction accuracy was assessed assuming a sampling time at 0 min, which presents the worst-case scenario of deviation. Goodness-of-fit plots improved by delaying the sampling time by 1 and 2 min (Fig. 6), which would be more coherent with other studies. However, the numerical evaluation for bias and precision also indicated a limited impact of the initial plasma concentrations on the overall results [loading dose (0 min) AFE/MRD 1.06/1.69, (1 min) 1.02/1.64, (2 min) 1.01/1.63; loading dose and maintenace infusion (0 min) 1.05/1.42, (1 min) 1.01/1.38, (2 min) 1.01/1.39]. Nonetheless, this issue repeatedly highlights the importance of accurately recording and reporting sampling times and dosing for informative pharmacokinetic and pharmacodynamic modelling as previously discussed by Sun et al. [84]. Also, the relative deviation from the line of identity with increasing milrinone plasma concentrations reflects the high inter-individual variability of milrinone plasma concentrations following the same dosing regimen in clinical practice. This has been previously highlighted by Bailey et al. [7]. The population-based PBPK drug–disease model was, however, capable of embracing this variability, i.e. 86 % of the milrinone plasma concentrations from paediatric patients without LCOS were within the 5th and 95th prediction interval.

The extent of pathophysiological parameters in the present model goes beyond published disease modelling in paediatric patients with open heart surgery, which included cardiopulmonary bypass and ventricle physiology as a covariate or cardiopulmonary bypass as a categorical variable in classical population pharmacokinetic models for pentobarbital [85], dexmedetomidine [86] and aprotinin [87]. Consequently, the present PBPK drug–disease model can be used to understand the impact of disease, surgery and age on the pharmacokinetics of milrinone. It indicates that organ function differs between paediatric patients with and without LCOS after surgery but also between adult and paediatric patients to an extent that precludes the administration of equal bodyweight-based dosing regimens to achieve comparable drug exposure.

The evaluation of milrinone prescribing for LCOS prevention indicated that neither dosing in accordance with PRIMACORP [12] nor dosing reflecting European hospital practice [4] seem to maintain the therapeutic target range of milrinone 100–300 ng/mL across the entire paediatric age range (Fig. 5). Neonates aged 14 days were predicted to have twofold higher steady-state plasma concentrations than children aged 2 years following a maintenance infusion of 0.5 μg/kg/min, which is in line with the practitioner view that neonates may require lower milrinone dosing than older children [88]. In addition, the present results underline the need for a loading dose, as previously highlighted by Bailey et al. [7]. A maintenance infusion of 0.5 μg/kg/min without loading would reach therapeutic plasma concentrations after 2 h, losing valuable time for preventing the drop in cardiac output expected to be clinically noticeable at 6–18 h post-surgery and the hallmark of LCOS [12, 89].

As with LCOS prevention, the evaluation of milrinone prescribing for LCOS treatment also indicated the need for improved dosing (Fig. 5). Although the recommended maintenance infusion of 0.25–0.75 μg/kg/min [11] would provide adequate exposure for all paediatric age groups,

clinicians are left alone with the important question of which dose to select for which paediatric patient in an acute intensive care setting. The advice in the prescribing guidance to consider the results of pharmacokinetic studies for dose selection becomes redundant when the information given on increased milrinone clearance with age does not distinguish between different age groups, modelling techniques and disease states.

Consequently, optimised dosing regimens were developed for LCOS treatment and prevention in paediatric patients, which will support clinicians and ensure safe and effective prescribing of milrinone (Fig. 5; Table 6). The dosing regimens were stratified into six age clusters that finally considered the differences in drug exposure due to age and pre- and postoperative organ function. The proposed regimens can be backed by research by Garcia Guerra et al. [10] and Zuppa et al. [90] that demonstrated similar milrinone dosing for 4-month-old infants and neonates/preterms, respectively, to reach the therapeutic target range. The extended loading dose over 60 min is an essential component of the optimised dosing regimen to ensure therapeutic plasma concentrations without delay but also to reduce the risk of initial hypotension as feared by clinicians [78, 79].

PBPK modelling is, however, limited to the available knowledge on physiology, pharmacology and compound characteristics, and our understanding of growth and maturation of organ function [23]. This also became apparent during model development, which led to the inclusion of assumption to fill the gaps of knowledge as explained in the Methods section. For example, assumptions had to be made at drug level, such as enzyme selection for the hepatic metabolism of milrinone, and at disease level, such as using the surrogate marker KIM-1 for the description of proximal tubular damage and reduced tubular secretion activity. However, the in-depth evaluation in healthy young adults as well as adult and paediatric patients including different ethnicities supports the validity of the results. In contrast, the advantage of the system–biology approach lies in its flexibility, and as soon as new data are available, it can be readily integrated into the PBPK drug–disease model for milrinone towards an improved description of the altered pharmacokinetics in diseased patients. Another limitation of the PBPK drug–disease model is its population-based character, which presents average dosing recommendation for different paediatric age groups but initially precludes dose individualisation based on patient-specific parameters. Nonetheless, this model-based dosing for paediatric patients with LCOS is an advancement on current standards because the threefold dose range for the milrinone maintenance infusion of 0.25–0.75 μg/kg/min in the SmPC irrespective of the patient's age was successfully reduced to a factor of 2 due to age-group stratification and implementation of disease characteristics. Given its superior performance over the models by Bailey et al. [7, 8] using NONMEM techniques, the results from the PBPK drug–disease model presented here provide a rational starting point for dose selection in clinical practice where no better information is available. However, model refinement should be endeavoured in the future, for which Bayesian forecasting may provide an appropriate means for dose individualisation. This is especially true for drugs showing a high interindividual variability in drug exposure, such as milrinone (Fig. 4). Successful examples of adopting Bayesian forecasting have been previously shown for warfarin using traditional pharmacokinetic models [91] but also for pravastatin using a PBPK drug model [92]. In addition, PK-Sim® itself provides the means for dose individualisation by step-wise replacement of population-based parameter estimates with patient-specific values, such as haematocrit and drug-specific clearances from bedside monitoring.

Understanding the pharmacokinetics and pharmacodynamics of milrinone is key for safe and effective prescribing practice. At the moment, prescribing is associated with a high rate of sub- and supratherapeutic plasma concentrations [10], adverse drug reactions [93] and prescribing errors [94]. The erroneous use of milrinone, in turn, has an increased risk of causing significant patient harm given that it is considered to be a high-alert medication [95]. Consequently, the findings of the present study have three important implications for future prescribing of milrinone, which are hoped to positively impact drug treatment. Firstly, drug dosing in paediatric patients needs to be age stratified to ensure comparable drug exposure across the entire paediatric age group. Secondly, paediatric patients with LCOS after open heart surgery require lower maintenance infusion doses than haemodynamically stabilised patients of a similar age, and thirdly, optimised dosing for LCOS treatment and prevention differs between adult and paediatric patients and precludes adult dose scaling attempts. From a wider perspective, the study demonstrated the potential use of PBPK drug–disease modelling to optimise dosing strategies for paediatric patients and will encourage its future adaptation to address other paediatric drug labelling deficits, which is in keeping with the view of regulatory authorities [96–98]. Equally important, the study also demonstrated the feasibility and benefit of data sharing between industry and academia. Complementary knowledge on the pharmacokinetics of drugs was gathered by the re-analysis of existing pharmacokinetic data using a new technique instead of setting up another clinical trial, which maximises the gain of information from available data and, at the same time, sets the risk of patients to zero [99]. Finally, clinical practice evaluation and PBPK drug–disease model extension to embrace other commonly used drugs for LCOS will further show the usefulness and applicability of the herein presented model.

In conclusion, the PBPK drug–disease model for milrinone in paediatric patients with and without LCOS after open heart surgery provides insight into the differences of drug exposure due to age and disease and, thus, allows the discrepancies among prescribing guidance, evidence from clinical studies and clinical practice pattern to be addressed. The evaluation of current milrinone prescribing indicated suboptimal achievement of the therapeutic target range of milrinone across all paediatric age groups and optimised dosing regimens are proposed to improve patient care by ensuring safe and effective prescribing.

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References

1. Ma M, Gauvreau K, Allan CK, et al. Causes of death after congenital heart surgery. Ann Thorac Surg. 2007;83:1438–45.
2. Shi S, Zhao Z, Liu X, et al. Perioperative risk factors for prolonged mechanical ventilation following cardiac surgery in neonates and young infants. Chest. 2008;134:768–74.
3. Vogt W, Läer S. Treatment for paediatric low cardiac output syndrome: results from the European EuLoCOS-Paed survey. Arch Dis Child. 2011;96:1180–6.
4. Vogt W, Läer S. Prevention for pediatric low cardiac output syndrome: results from the European survey EuLoCOS-Paed. Paediatr Anaesth. 2011;12:1176–84.
5. Vogt W, Läer S. Drug use patterns for the prevention of paediatric low cardiac output syndrome in Europe. Intensive Care Med. 2011;37:1390–1.
6. Milrinone: Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended (2011). http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Paediatric_Regulation/Assessment_Reports/Article_45_work-sharing/Milrinone-_2011_06_Art.45PaedPdAR.pdf. Accessed 9 Jun 2013.
7. Bailey JM, Hoffman TM, Wessel DL, et al. A population pharmacokinetic analysis of milrinone in pediatric patients after cardiac surgery. J Pharmacokinet Pharmacodyn. 2004;31:43–59.
8. Bailey JM, Miller BE, Lu W, et al. The pharmacokinetics of milrinone in pediatric patients after cardiac surgery. Anesthesiology. 1999;90:1012–8.
9. Ramamoorthy C, Anderson GD, Williams GD, et al. Pharmacokinetics and side effects of milrinone in infants and children after open heart surgery. Anesth Analg. 1998;86:283–9.
10. Garcia Guerra G, Senthilselvan A, Kutsogiannis DJ, et al. Safe administration of milrinone. Pediatr Crit Care Med. 2011;12:A11–A12.
11. Sanofi aventis. Summary of Product Characteristics for Primacor 1 mg/ml solution for injection (INN: Milrinone).http://www.medicines.org.uk/EMC/medicine/6984/SPC/Primacor+1mg+ml+Solution+for+Injection/. Accessed 9 Jul 2012.
12. Hoffman TM, Wernovsky G, Atz AM, et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation. 2003;107:996–1002.
13. Edginton AN, Willmann S. Physiology-based simulations of a pathological condition: prediction of pharmacokinetics in patients with liver cirrhosis. Clin Pharmacokinet. 2008;47:743–52.
14. Johnson TN, Boussery K, Rowland-Yeo K, et al. A semi-mechanistic model to predict the effects of liver cirrhosis on drug clearance. Clin Pharmacokinet. 2010;49:189–206.
15. Yeo KR, Aarabi M, Jamei M, et al. Modelling and predicting drug pharmacokinetics in patients with renal impairment. Expert Opin Clin Pharmacol. 2011;4:261–74.
16. Zhao P, de Vieira MLT, Grillo JA, et al. Evaluation of exposure change of nonrenally eliminated drugs in patients with chronic kidney disease using physiologically based pharmacokinetic modeling and simulation. J Clin Pharmacol. 2012;52:91S–108S.
17. Björkman S, Wada DR, Berling BM, et al. Prediction of the disposition of midazolam in surgical patients by a physiologically based pharmacokinetic model. J Pharm Sci. 2001;90:1226–41.
18. Johnson TN, Rostami-Hodjegan A, Tucker GT. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. Clin Pharmacokinet. 2006;45:931–56.
19. Edginton AN, Schmitt W, Willmann S. Development and evaluation of a generic physiologically based pharmacokinetic model for children. Clin Pharmacokinet. 2006;45:1013–34.
20. Parrott N, Davies B, Hoffmann G, et al. Development of a physiologically based model for oseltamivir and simulation of pharmacokinetics in neonates and infants. Clin Pharmacokinet. 2011;50:613–23.
21. Björkman S. Prediction of drug disposition in infants and children by means of physiologically based pharmacokinetic (PBPK) modelling: theophylline and midazolam as model drugs. Br J Clin Pharmacol. 2005;59:691–704.
22. Rowland M, Peck C, Tucker G. Physiologically-based pharmacokinetics in drug development and regulatory science. Annu Rev Pharmacol Toxicol. 2011;51:45–73.
23. Barrett JS, Della Casa Alberighi O, Läer S, et al. Physiologically based pharmacokinetic (PBPK) modeling in children. Clin Pharmacol Ther. 2012;92:40–9.
24. Willmann S, Höhn K, Edginton A, et al. Development of a physiology-based whole-body population model for assessing the influence of individual variability on the pharmacokinetics of drugs. J Pharmacokinet Pharmacodyn. 2007;34:401–31.
25. Zhang Y, Huo M, Zhou J, et al. PKSolver: an add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel. Comput Methods Programs Biomed. 2010;99:306–14.
26. Stroshane RM, Koss RF, Biddlecome CE, et al. Oral and intravenous pharmacokinetics of milrinone in human volunteers. J Pharm Sci. 1984;73:1438–41.
27. Young RA, Ward A. Milrinone: a preliminary review of its pharmacological properties and therapeutic use. Drugs. 1988;36:158–92.
28. Alousi AA, Fabian RJ, Baker JF, et al. Milrinone. In: Scriabine A, editor. New drugs annual: cardiovascular drugs, vol. 3. New York: Raven Press; 1985. p. 245–83.
29. Coleman MD. Human drug metabolism: an introduction. 2nd ed. New York: Wiley; 2010.
30. Tukey RH, Strassburg CP. Human UDP-glucuronosyltransferases: metabolism, expression, and disease. Annu Rev Pharmacol Toxicol. 2000;40:581–616.

31. Woolfrey SG, Hegbrant J, Thysell H, et al. Dose regimen adjustment for milrinone in congestive heart failure patients with moderate and severe renal failure. J Pharm Pharmacol. 1995;47:651–5.
32. National Kidney Foundation. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis. 2002;39:S46–75.
33. Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. J Clin Invest. 1950;29:496–507.
34. Feneck RO. Effects of variable dose milrinone in patients with low cardiac output after cardiac surgery. European Multicenter Trial Group. Am Heart J. 1991;121:1995–9.
35. Monnet X, Persichini R, Ktari M, et al. Precision of the transpulmonary thermodilution measurements. Crit Care. 2011; 15:R204.
36. Stetz CW, Miller RG, Kelly GE, et al. Reliability of the thermodilution method in the determination of cardiac output in clinical practice. Am Rev Respir Dis. 1982;126:1001–4.
37. Arnold JM, Ludmer PL, Wright RF, et al. Role of reflex sympathetic withdrawal in the hemodynamic response to an increased inotropic state in patients with severe heart failure. J Am Coll Cardiol. 1986;8:413–8.
38. Cinequegrani M, Mesner C, Baggs JG, et al. Effects of continuous milrinone infusion on forearm and hepatic blood flows. Clin Res. 1984;32:155A.
39. Tobata D, Takao K, Mochizuki M, et al. Effects of dopamine, dobutamine, amrinone and milrinone on regional blood flow in isoflurane anesthetized dogs. J Vet Med Sci. 2004;66:1097–105.
40. Chen EP, Bittner HB, Davis RD, et al. Milrinone improves pulmonary hemodynamics and right ventricular function in chronic pulmonary hypertension. Ann Thorac Surg. 1997;63: 814–21.
41. Sulek CA, Blas ML, Lobato EB. Milrinone increases middle cerebral artery blood flow velocity after cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 2002;16:64–9.
42. Cooper KE, Edholm OG, Mottram RF. The blood flow in skin and muscle of the human forearm. J Physiol. 1955;128:258–67.
43. Willmann S, Lippert J, Schmitt W. From physicochemistry to absorption and distribution: predictive mechanistic modelling and computational tools. Expert Opin Drug Metab Toxicol. 2005;1:159–68.
44. Hillman RS, Ault K, Rinder H. Hematology in clinical practice. 4th ed. New York: McGraw-Hill; 2005.
45. Tietz NW. Clinical guide to laboratory tests. 3rd ed. Philadelphia: W.B. Saunders & Co.; 1995.
46. Williams LR. Reference values for total blood volume and cardiac output in humans. Washington, DC: Department of Energy; 1994.
47. Greenblatt DJ, Harmatz JS, Shader RI. Clinical pharmacokinetics of anxiolytics and hypnotics in the elderly: therapeutic considerations (part I). Clin Pharmacokinet. 1991;21:165–77.
48. Greenblatt DJ, Harmatz JS, Shader RI. Clinical pharmacokinetics of anxiolytics and hypnotics in the elderly: therapeutic considerations (part II). Clin Pharmacokinet. 1991;21:262–73.
49. Zappitelli M, Bernier P, Saczkowski RS, et al. A small postoperative rise in serum creatinine predicts acute kidney injury in children undergoing cardiac surgery. Kidney Int. 2009;76:885–92.
50. Han WK, Wagener G, Zhu Y, et al. Urinary biomarkers in the early detection of acute kidney injury after cardiac surgery. Clin J Am Soc Nephrol. 2009;4:873–82.
51. Han WK, Waikar SS, Johnson A, et al. Urinary biomarkers in the early diagnosis of acute kidney injury. Kidney Int. 2008; 73:863–9.
52. Krawczeski CD, Goldstein SL, Woo JG, et al. Temporal relationship and predictive value of urinary acute kidney injury biomarkers after pediatric cardiopulmonary bypass. J Am Coll Cardiol. 2011;58:2301–9.
53. Bernstein D, Teitel D, Sidi D, et al. Redistribution of regional blood flow and oxygen delivery in experimental cyanotic heart disease in newborn lambs. Pediatr Res. 1987;22:389–93.
54. Jonas RA, Wypij D, Roth SJ, et al. The influence of hemodilution on outcome after hypothermic cardiopulmonary bypass: results of a randomized trial in infants. J Thorac Cardiovasc Surg. 2003;126:1765–74.
55. McNamara PJ, Alcorn J. Protein binding predictions in infants. AAPS PharmSci. 2002;4:19–26.
56. Chang AC, Atz AM, Wernovsky G, et al. Milrinone: systemic and pulmonary hemodynamic effects in neonates after cardiac surgery. Crit Care Med. 1995;23:1907–14.
57. Hayton WL. Maturation and growth of renal function: dosing renally cleared drugs in children. AAPS PharmSci. 2000;2:22–8.
58. Edginton AN, Schmitt W, Voith B, et al. A mechanistic approach for the scaling of clearance in children. Clin Pharmacokinet. 2006;45:683–704.
59. Tsunoo M, Momomura S, Imai Y, et al. Safety, tolerance and pharmacokinetics of milrinone in phase I study in healthy male Japanese subjects (2)—after intravenous infusion. Jpn Pharmacol Ther. 1993;21:201–21.
60. Bailey JM, Levy JH, Kikura M, et al. Pharmacokinetics of intravenous milrinone in patients undergoing cardiac surgery. Anesthesiology. 1994;81:616–22.
61. Butterworth JF, Hines RL, Royster RL, et al. A pharmacokinetic and pharmacodynamic evaluation of milrinone in adults undergoing cardiac surgery. Anesth Analg. 1995;81:783–92.
62. Das PA, Skoyles JR, Sherry KM, et al. Disposition of milrinone in patients after cardiac surgery. Br J Anaesth. 1994;72:426–9.
63. de Hert SG, Moens MM, Jorens PG, et al. Comparison of two different loading doses of milrinone for weaning from cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 1995;9:264–71.
64. Hasei M, Uchiyama A, Nishimura M, et al. Correlation between plasma milrinone concentration and renal function in patients with cardiac disease. Acta Anaesthesiol Scand. 2008;52:991–6.
65. Benotti JR, Hood WB. Dose-ranging study of intravenous milrinone to determine efficacy and pharmacokinetics. In: Braunwald E, editor. Milrinone: investigation of new inotropic therapy for congestive heart failure. New York: Raven Press; 1984. p. 95–107.
66. Androne A, Katz SD, Lund L, et al. Hemodilution is common in patients with advanced heart failure. Circulation. 2003;107: 226–9.
67. Fichtl B, Meister W, Schmied R. Serum protein binding of drugs is not altered in patients with severe chronic cardiac failure. Int J Clin Pharmacol Ther Toxicol. 1983;21:241–4.
68. Ogden CL, Fryar CD, Carroll MD, et al. Mean body weight, height, and body mass index, United States 1960–2002. Adv Data. 2004;347:1–17.
69. World Health Organization. The WHO child growth standards. http://www.who.int/childgrowth/standards/en/. Accessed 12 Jul 2012.
70. World Health Organization. Growth reference data for 5-19 years. http://www.who.int/growthref/en/. Accessed 10 Jul 2012.
71. Habib RH, Zacharias A, Schwann TA, et al. Adverse effects of low hematocrit during cardiopulmonary bypass in the adult: should current practice be changed? J Thorac Cardiovasc Surg. 2003;125:1438–50.
72. Dorne JL, Walton K, Renwick AG. Human variability in glucuronidation in relation to uncertainty factors for risk assessment. Food Chem Toxicol. 2001;39:1153–73.

73. Dorne JL, Walton K, Renwick AG. Human variability in the renal elimination of foreign compounds and renal excretion-related uncertainty factors for risk assessment. Food Chem Toxicol. 2004;42:275–98.
74. Ito K, Houston JB. Prediction of human drug clearance from in vitro and preclinical data using physiologically based and empirical approaches. Pharm Res. 2005;22:103–12.
75. Jones HM, Parrott N, Jorga K, et al. A novel strategy for physiologically based predictions of human pharmacokinetics. Clin Pharmacokinet. 2006;45:511–42.
76. Clewell HJ, Andersen ME. Use of physiologically based pharmacokinetic modeling to investigate individual versus population risk. Toxicology. 1996;111:315–29.
77. Cameron JW, Rosenthal A, Olson AD. Malnutrition in hospitalized children with congenital heart disease. Arch Pediatr Adolesc Med. 1995;149:1098–102.
78. Brierley J, Peters M. Hemodynamics of milrinone loading in critically ill children. Crit Care Med. 2006;32:A63.
79. Brierley J, Carcillo JA, Choong K, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med. 2009;37:666–88.
80. Benotti JR, Lesko LJ, McCue JE, et al. Pharmacokinetics and pharmacodynamics of milrinone in chronic congestive heart failure. Am J Cardiol. 1985;56:685–9.
81. Fitzpatrick PG, Cinquegrani MP, Vakiener AR, et al. Hemodynamic and regional blood flow response to milrinone in patients with severe congestive heart failure: a dose-ranging study. Am Heart J. 1987;114:97–105.
82. Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. Clin Pharmacokinet. 1997;32:101–19.
83. Li F, Nandy P, Chien S, et al. Pharmacometrics-based dose selection of levofloxacin as a treatment for postexposure inhalational anthrax in children. Antimicrob Agents Chemother. 2010;54(1):375–9.
84. Sun H, Ette EI, Ludden TM. On the recording of sample times and parameter estimation from repeated measures pharmacokinetic data. J Pharmacokinet Biopharm. 1996;24:637–50.
85. Zuppa AF, Nicolson SC, Barrett JS, et al. Population pharmacokinetics of pentobarbital in neonates, infants, and children after open heart surgery. J Pediatr 2011;159:414–419.e1–3.
86. Su F, Nicolson SC, Gastonguay MR, et al. Population pharmacokinetics of dexmedetomidine in infants after open heart surgery. Anesth Analg. 2010;110:1383–92.
87. Tae Y, Kwak JG, Kim B, et al. Population pharmacokinetic analysis and dosing regimen optimization of aprotinin in neonates and young infants undergoing cardiopulmonary bypass. J Clin Pharmacol. 2011;51:1163–76.
88. van Saet A, de Wildt SN. Prevention of low cardiac output syndrome in children: where is the evidence? Paediatr Anaesth. 2011;21:1173–5.
89. Massé L, Antonacci M. Low cardiac output syndrome: identification and management. Crit Care Nurs Clin North Am. 2005;17:375–83.
90. Zuppa AF, Nicolson SC, Adamson PC, et al. Population pharmacokinetics of milrinone in neonates with hypoplastic left heart syndrome undergoing stage I reconstruction. Anesth Analg. 2006;102:1062–9.
91. Wright DFB, Duffull SB. A Bayesian dose-individualization method for warfarin. Clin Pharmacokinet. 2013;52:59–68.
92. Krauss M, Burghaus R, Lippert J, et al. Using Bayesian-PBPK modeling for assessment of inter-individual variability and subgroup stratification. In Silico Pharmacol. 2013. doi: 10.1186/2193-9616-1-6.
93. Watson S, Christian KG, Churchwell KB. Side effects of milrinone in the cardiac PICU. Clin Intensive Care. 1999;10:149.
94. Martinez-Anton A, Sanchez JI, Casanueva L. Impact of an intervention to reduce prescribing errors in a pediatric intensive care unit. Intensive Care Med. 2012;38:1532–8.
95. Institute for Safe Medication Practices. ISMP's list of high-alert medications. https://www.ismp.orgtoolshighalertmedications.pdf. Accessed 1 July 2013.
96. Manolis E, Pons G. Proposals for model-based paediatric medicinal development within the current European Union regulatory framework. Br J Clin Pharmacol. 2009;68:493–501.
97. Jönnson S, Henningsson A. Medical Products Agency, Uppsala, Sweden. Regulatory vision of paediatric applications. http://www.emea.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500009845.pdf. Accessed 12 Jul 2012.
98. Zhao P, Zhang L, Grillo JA, et al. Applications of physiologically based pharmacokinetic (PBPK) modeling and simulation during regulatory review. Clin Pharmacol Ther. 2011;89:259–67.
99. Anderson BJ, Merry AF. Data sharing for pharmacokinetic studies. Paediatr Anaesth. 2009;19:1005–10.
100. Knox C, Law V, Jewison T, et al. DrugBank 3.0: a comprehensive resource for 'omics' research on drugs. Nucleic Acids Res. 2011;39:D1035–41.
101. Altomare C, Cellamare S, Summo L, et al. Ionization behaviour and tautomerism-dependent lipophilicity of pyridine-2(1H)-one cardiotonic agents. Bioorg Med Chem. 2000;8:909–16.
102. de Candia M, Fossa P, Cellamare S, et al. Insights into structure-activity relationships from lipophilicity profiles of pyridin-2(1H)-one analogs of the cardiotonic agent milrinone. Eur J Pharm Sci. 2005;26:78–86.
103. Maganti M, Badiwala M, Sheikh A, et al. Predictors of low cardiac output syndrome after isolated mitral valve surgery. J Thorac Cardiovasc Surg. 2010;140:790–6.
104. Maganti MD, Rao V, Borger MA, et al. Predictors of low cardiac output syndrome after isolated aortic valve surgery. Circulation. 2005;112:I448–52.
105. Vánky FB, Håkanson E, Tamás E, et al. Risk factors for postoperative heart failure in patients operated on for aortic stenosis. Ann Thorac Surg. 2006;81:1297–304.
106. Arribas Leal JM, Pascual DA, et al. Epidemiology and new predictors of low cardiac output syndrome after isolated coronary artery bypass grafting. Eur Heart J. 2010;31:68–9.
107. McKinlay KH, Schinderle DB, Swaminathan M, et al. Predictors of inotrope use during separation from cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 2004;18:404–8.
108. Müller M, Junger A, Bräu M, et al. Incidence and risk calculation of inotropic support in patients undergoing cardiac surgery with cardiopulmonary bypass using an automated anaesthesia record-keeping system. Br J Anaesth. 2002;89:398–404.
109. Butterworth JF, Legault C, Royster RL, et al. Factors that predict the use of positive inotropic drug support after cardiac valve surgery. Anesth Analg. 1998;86:461–7.
110. Rao V, Ivanov J, Weisel RD, et al. Predictors of low cardiac output syndrome after coronary artery bypass. J Thorac Cardiovasc Surg. 1996;112:38–51.
111. Jungbauer CG, Birner C, Jung B, et al. Kidney injury molecule-1 and N-acetyl-β-D-glucosaminidase in chronic heart failure: possible biomarkers of cardiorenal syndrome. Eur J Heart Fail. 2011;13:1104–10.
112. Ochs HR, Schuppan U, Greenblatt DJ, et al. Reduced distribution and clearance of acetaminophen in patients with congestive heart failure. J Cardiovasc Pharmacol. 1983;5:697–9.
113. Miners JO, Mackenzie PI. Drug glucuronidation in humans. Pharmacol Ther. 1991;51:347–69.
114. Ng CY, Ghabrial H, Morgan DJ, et al. Right heart failure impairs hepatic elimination of p-nitrophenol without inducing changes in content or latency of hepatic UDP-glucuronosyltransferases. J Pharmacol Exp Ther. 2000;295:830–5.

115. Ljungman S, Laragh JH, Cody RJ. Role of the kidney in congestive heart failure: relationship of cardiac index to kidney function. Drugs. 1990;39:10–21.
116. Leithe ME, Margorien RD, Hermiller JB, et al. Relationship between central hemodynamics and regional blood flow in normal subjects and in patients with congestive heart failure. Circulation. 1984;69:57–64.
117. Zelis R, Flaim SF. Alterations in vasomotor tone in congestive heart failure. Prog Cardiovasc Dis. 1982;24:437–59.
118. Feneck RO, Sherry KM, Withington PS, et al. Comparison of the hemodynamic effects of milrinone with dobutamine in patients after cardiac surgery. J Cardiothorac Vasc Anesth. 2001;15:306–15.
119. Hiraoka H, Yamamoto K, Okano N, et al. Changes in drug plasma concentrations of an extensively bound and highly extracted drug, propofol, in response to altered plasma binding. Clin Pharmacol Ther. 2004;75:324–30.
120. Lee E, Chin J, Choi D, et al. Postoperative hypoalbuminemia is associated with outcome in patients undergoing off-pump coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth. 2011;25:462–8.
121. Wijeysundera DN, Rao V, Beattie WS, et al. Evaluating surrogate measures of renal dysfunction after cardiac surgery. Anesth Analg. 2003;96:1265–73.
122. Palomba H, de Castro I, Neto ALC, et al. Acute kidney injury prediction following elective cardiac surgery: AKICS score. Kidney Int. 2007;72:624–31.
123. Llopart T, Lombardi R, Forselledo M, et al. Acute renal failure in open heart surgery. Ren Fail. 1997;19:319–23.
124. Shim CK, Sawada Y, Iga T, et al. Estimation of renal secretory function for organic cations by endogenous N1-methylnicotinamide in rats with experimental renal failure. J Pharmacokinet Biopharm. 1984;12:23–42.
125. Park JM, Lin YS, Calamia JC, et al. Transiently altered acetaminophen metabolism after liver transplantation. Clin Pharmacol Ther. 2003;73:545–53.
126. Subramanian RM, Chandel N, Budinger GRS, et al. Hypoxic conformance of metabolism in primary rat hepatocytes: a model of hepatic hibernation. Hepatology. 2007;45:455–64.
127. Ruokonen E, Takala J, Kari A. Regional blood flow and oxygen transport in patients with the low cardiac output syndrome after cardiac surgery. Crit Care Med. 1993;21:1304–11.
128. Bulkley GB, Oshima A, Bailey RW. Pathophysiology of hepatic ischemia in cardiogenic shock. Am J Surg. 1986;151:87–97.
129. Hall C, Mørkrid L, Kjekshus J. Redistribution of peripheral blood flow during acute left ventricular failure in the dog. Scand J Clin Lab Invest. 1988;48:785–94.
130. Smiseth OA, Riemersma RA, Steinnes K, et al. Regional blood flow during acute heart failure in dogs. Role of adipose tissue perfusion in regulating plasma-free fatty acids. Scand J Clin Lab Invest. 1983;43:285–92.
131. Sapirstein LA, Sapirstein EH, Bredemeyer A. Effect of hemorrhage on the cardiac output and its distribution in the rat. Circ Res. 1960;8:135–48.

Supplementary table 1 Patient characteristics in the studies used for the assessment of the predictive performance of the physiology-based pharmacokinetic drug-disease model

Study	Number of subjects	Age (years)	Weight (kg)	Height (cm)	Male (%)	Ethnicity/ Country of study conduct	Sampling site	Cardiac functioning before milrinone administration	Dosing[a]	Vasoactive drugs	Evidence of renal/hepatic impairment
Healthy adults											
Stroshane	21	30±6	73±10	NR	100	NR/US	NR	No cardiac dysfunction	**B 25-125**	No	No/No
Tsunoo	9	23±1	64±9	173±5	100	Japanese/ Japan	NR	No cardiac dysfunction	B 50 (10) ± **M** 0.5-**1** (2h)	No	No/No
Adult patients with heart failure and no open heart surgery											
Benotti	11	61±10	NR	NR	82	NR/US	NR	CI 2.5±0.9 and PCWP 21±7, NYHA III-IV	**M 0.20, 0.45 or 0.75** (18)	NR	Creatinine <3 /No
Adult patients without LCOS											
Butterworth	19	26-86	93±16	NR	58	NR/US	Arterial	No need for postoperative inotropic support or IABP and CI < 3	**B 25-75 (1)**	No	Creatinine < 2 /NR
Bailey I	25	61±10	87±18	175±9	76	NR/US	Arterial	Haemodynamically stable during and after separation from CPB with CI ≤ 2.5 and PCWP ≤ 18	**B** 25, **50**, 75 ± **M 0.5** (16)	Yes	No/No
Adult patients with LCOS											
Das	6	58±20	58±7	163±5	43	NR/UK	Arterial	Need for postoperative inotropic support with CI ≤ 2 and PCWP ≥ 10	**B 50 (10) + M 0.5** (≥ 5)	No	No/No
De Heert	20	64±10	74±14	165±9	65	NR/Belgium	NR	CI 1.7±0.7 and PCWP 19.5±3.2	**B 20/40 (15) + M 0.5** (≥4)	Yes	No/No
Hasei	10	62±16	62±7	158±13	60	NR/Japan	NR	Need for postoperative inotropic support	**M 0.2 (≥48)**	NR	eGFR 60±31 /NR
Paediatric patients without LCOS											
Bailey II (Bolus)	8	0.7±0.5	6.7±3.0	NR	NR	NR/US	Arterial	Haemodynamically stable post surgery with CI 2.9±0.9	**B 50 (5)**	Yes	NR/NR
Bailey II (Bolus+Infusion)	12	0.8±0.5	7.1±3.0						**B 50 (5) + M 0.5** (16 h)		
Bailey III (0-1m)	46	0.6±1.1	5.8±3.6	NR	57	74% White/US	NR	No LCOS or hypotension on arrival at ICU	**B 25/75 (60) + M 0.25/0.75** (35)	Yes	Creatinine < 1.5 before surgery/NR
Bailey III (1-24m)	93										
Bailey III (2-8y)	18										
Paediatric patients with LCOS											
Ramamoorthy	19	3±3.7	12±12	NR	NR	NR/US	NR	Need for postoperative inotropic support	**B 25 (5)/50 (10) + M 0.25/0.5 (0.5) + B 25/25 + M 0.5/0.75** (≈ 40)	NR	NR/NR

Data presentation, units and abbreviations: Summary data in mean ± SD or range; NR for not reported; B, Bolus infusion in µg/kg (duration of drug administration in min); M, Maintenance infusion in µg/kg per min (duration of drug administration in h); CI, Cardiac index in L/min per m^2; PCWP, Pulmonary capillary wedge pressure in mmHg; NYHA; New York Heart Heart Association Classification for heart failure; Creatinine in mg/dl; IABP, intraaortic balloon pump; eGFR, Estimated glomerular filtration rate in ml/min per 1.73m^2.

[a] Dosing regimens highlighted in bold were used for the assessment of the predictive performance of the physiology-based pharmacokinetic drug-disease model.

Supplementary table 2 Description of the observed plasma concentration data used for model evaluation

Study	Plasma concentrations			
	Profile	Data presentation	N	Sources
Healthy adults				
Stroshane	P+E	Individual	180	MA holder
Tsunoo	M+E	Mean	11	Plot digitization
Adult patients with heart failure				
Benotti	M+E	Mean	49	Plot digitization
Adult patients without LCOS				
Butterworth	P+E	Individual	321	Author
Bailey I	P+M	Individual	55	Plot digitization
Adult patients with LCOS				
Das	P+M+E	Individual	131	Plot digitization
De Heert (low dose)	P+M	Mean	13	Plot digitization
De Heert (high dose)	P+M	Mean	13	Plot digitization
Hasei	M	Individual	40	Author
Paediatric patients without LCOS				
Bailey II (Bolus)	P+E	Individual	89	Author
Bailey II (Bolus + Infusion)	P+M	Individual	109	Author
Bailey III (0-1m)	P+M	Individual	72	MA holder
Bailey III (1-24m)	P+M	Individual	120	MA holder
Bailey III (2-8y)	P+M	Individual	16	MA holder
Paediatric patients with LCOS				
Ramamoorthy	-	-	-	-
Bailey III (0-1m)	P+M	Individual	5	MA holder
Bailey III (1-24m)	P+M	Individual	30	MA holder
Bailey III (2-8y)	P+M	Individual	5	MA holder

Abbreviations: N, Total number of plasma concentrations (from mean curves or individual curves times patients investigated) used for model evaluation; P, plasma concentrations representing the peak concentration after a loading dose; E, plasma concentrations representing the elimination period after a loading dose or maintenance infusion; M, plasma concentrations representing the profile following a maintenance infusion dose ± steady-state conditions; MA holder, marketing authorisation holder.

Chapter 5

GENERAL DISCUSSION

The results presented in this thesis provide comprehensive information about current drug therapy for LCOS in paediatric patients with open heart surgery across Europe. The assessment of this prescribing pattern enabled the identification of paediatric research needs. The most potential drug, milrinone, was embraced in a novel PBPK drug-disease model to better understand the influence of age, disease and surgery on drug exposure. This integrated approach directly resulted in age-appropriate optimised dosing strategies for milrinone towards safer and more effective drug therapy for paediatric LCOS.

Chapter 2 presents current drug treatment for paediatric LCOS and the use of prescribing resources resulting from the European survey on the pharmacological management of low cardiac output syndrome in paediatric patients with open heart surgery, short EuLoCOS-Paed, in which 90 of 125 eligible hospitals from 31 of 36 European countries participated between January and August 2009.

The initial treatment and subsequent add-on steps for the three different LCOS subtypes were reported as follows: For LCOS with elevated systemic vascular resistance with milrinone (34%) being preferred for the initial treatment step, epinephrine (24%) favoured for the first add-on step and levosimendan or epinephrine (22%) favoured for the second add-on step. LCOS with low systemic vascular resistance was mainly initiated with dopamine (20%), whereas epinephrine (29%) and norepinephrine (24%) were preferred for the first and second add-on step, respectively. Finally, milrinone (17%) was the preferred drug for the initial treatment for LCOS with elevated pulmonary vascular resistance, and subsequently combined with inhaled nitric oxide (20%) and prostacyclin derivatives (22%). In all, drug use was highly variable with up to 23 different drugs from nine therapeutic drug classes for a single LCOS subtype. Nonetheless, milrinone, epinephrine, dopamine and dobutamine were mostly reported for all LCOS subtypes, but only milrinone monotherapy for LCOS with elevated systemic vascular resistance was significantly more often reported than other drug regimens.

In addition, *Chapter 2* provides information about the use of prescribing resources for paediatric LCOS in European hospitals showing that standard hospital protocols were mostly consulted for prescribing. However, prescribing resources were stated to be insufficient by nearly half of the survey participants. The majority of participants would welcome clinical practice guidelines in this field.

Chapter 3 presents the second part of the results from EuLoCOS-Paed and provides information on the prescribing pattern and target patient group for paediatric LCOS prevention (*Chapter 3.1*) as well as individual drug use (*Chapter 3.2*). Merging the information with those obtained in *Chapter 2* gives comprehensive insight into the overall drug therapy for paediatric LCOS across Europe.

In *Chapter 3.1*, the analysis of the survey responses indicated that the majority of European hospitals administer preventive drug therapy and primarily target patients at risk but without a uniform risk stratification scheme. The drug therapy for LCOS prevention was also highly variable as

it has been already described for LCOS treatment in *Chapter 2*. In total, 24 different drug regimens were reported by 69 hospitals and of those, milrinone monotherapy (25% of all reports) or the combined use of milrinone with dopamine (12%), epinephrine (11%), dobutamine (9%) or levosimendan (7%) were reported in the majority of cases. Interestingly, a detailed analysis further demonstrated that milrinone monotherapy constituted higher loading but lower maintenance infusion doses than milrinone combination therapy.

Chapter 3.2 demonstrates that variability in drug use originates from both the drug combinations as shown in *Chapter 3.1* and the individual drugs. Seventeen drugs from seven therapeutic drug classes were identified from a total of 24 different drug regimens reported for LCOS prevention; only six drugs were reported more than twice: milrinone, dopamine, dobutamine, epinephrine, levosimendan and methylprednisolone. By far, milrinone was significantly more often reported than other drugs but it also displayed the highest variability: 15-fold and 7.5-fold differences were reported for the loading and maintenance infusion doses, respectively. The duration of drug administration varied by a factor of 28.

In *Chapter 4*, the successful development and evaluation of a novel population-based PBPK drug-disease model for paediatric patients in need for LCOS treatment or prevention after open heart surgery is presented. Milrinone was considered the ideal drug candidate to embrace in this model because *Chapter 2* and *Chapter 3* highlighted its importance within clinicians' drug armoury for paediatric LCOS but also its highly variable administration mode, which questions its safe and effective use. In addition, regulatory authorities have stressed the need for further pharmacokinetic investigations in paediatric patients.

The evaluation of milrinone's pharmacokinetics showed that its total plasma clearance is non-linearly dependent on paediatric age. In addition, pre- and postoperative organ function differently affects exposure in paediatric patients with and without LCOS but also in adults. The subsequent evaluation of approved milrinone dosing for LCOS treatment and current off-label dosing for LCOS prevention demonstrated that no regimen seems to provide an adequate exposure across all paediatric age groups. Similar results were also predicted for adult patients. Consequently, optimised dosing strategies were developed using the novel PBPK drug-disease model, which considered the exposure differences due to age and disease state:

- Dosing for paediatric patients is age-stratified into six clusters with the lowest dose predicted for the newborn period and the highest dose for patients aged 1-9 years.
- Optimised dosing includes a loading dose administered over 60 min. The dose itself does not differ between paediatric patients with and without LCOS but among the paediatric age clusters.

- Paediatric patients with LCOS need lower maintenance infusion doses than those without LCOS.
- Optimised dosing strategies for milrinone differ between adult and paediatric patients.

SOME QUESTIONS ABOUT VALIDITY AND RELIABILITY IN THIS RESEARCH

The work presented in this thesis led to the development of optimised dosing regimens for the drug with most potential for providing safer and more effective drug therapy for LCOS in paediatric patients – milrinone. To which extent, however, is the drug choice representative and actually reflects the paediatric needs in clinical practice? Furthermore, how plausible is the inclusion of milrinone in the PBPK drug-disease model? These aspects will be addressed to tackle research validity and reliability described in *Chapters 2 - 4*.

Bridging the time gap from EuLoCOS-Paed until now

EuLoCOS-Paed provided valid and reliable results on the European prescribing pattern for paediatric LCOS. Nonetheless, the question remains to which extent the results from 2009 are applicable to today's hospital practice. First of all, subsequent commentaries on EuLoCOS-Paed in 2011 and 2012 underlined the results and strengthened the role of milrinone in clinicians' drug armoury for paediatric LCOS [1, 2]. In addition, milrinone has been approved for the treatment of paediatric LCOS in 2011/2012 across Europe following the conclusions of the European Public Assessment Report [3], which may have even fostered its use. Nonetheless, levosimendan has also been discussed by clinicians to be potentially valuable for paediatric LCOS [2] and it has already replaced milrinone in the acute care of adult heart failure [4]. At the moment, limited European availability, higher treatment costs and non-superiority in reducing the incidence of LCOS [5] and cardiac index [6] compared to milrinone may hamper the frequent uptake of levosimendan in paediatric hospitals at the moment but it cannot be excluded in future. Drug use is not static – it is reflective of the currently available level of evidence, guideline recommendations, labelling status of drugs and cost/benefit analysis, all of which embark major deficits in paediatric cardiac surgery. Increased awareness of the deficits and focused research will ultimately change the picture of paediatric drug use. Thus, it is even more important to provide flexible and dynamic tools to support modelling and simulation towards improved paediatric dosing such as the herein presented PBPK drug-disease model.

Assessing paediatric needs

In *Chapter 2* and *3*, the drugs with the highest need for research in paediatric LCOS were identified based on the frequency reports in EuLoCOS-Paed, shared uptake for the LCOS subtypes and variability in the mode of drug administration. The status of drug approval did not influence decision-making, because all drugs, except dobutamine, were used off-label at the time of the survey conduct.

The licensing status of dobutamine, however, was not regarded to be sufficient for exclusion from the list because dosing guidance for dobutamine is insufficient [7] and the need for more research in neonates has already been stressed by regulatory authorities [8].

The work presented in *Chapter 2* and *3* partially reflects the results of the "Inventory of paediatric medicine: Cardiovascular therapeutic area" by the EMA [9], which has been based on the frequency analysis of off-label drug use surveyed across Europe and coupled with the existing list of paediatric needs established by the former Paediatric Working Party as previously described in *Chapter 1*. This coupling is essential to achieve meaningful recommendations because diseases with a low prevalence but clinical seriousness, such as LCOS, are underreported in the EMA survey. In contrast, the former Paediatric Working Party identified the needs in this field by collaborating with experts and concluded on an unprioritised list of drugs, which indeed included the therapeutic indications for LCOS and acute cardiac failure. In addition, the EMA realised a list for prioritising funding for research into drugs for conditions based on their clinical seriousness and lack of available treatment alternatives with a special focus on neonatal treatment [8]. Related drugs were identified from published therapeutic reviews and prioritised with regard to efficacy and safety. The drawback is that therapeutic reviews do not necessarily reflect clinical hospital practice albeit prepared from a public health perspective: the combined Medical Subject Heading (MeSH®) search in PubMed with "Infant" or "Infant, Newborn", "Low cardiac output syndrome" and "Review" resulted in 13 publications, of which only one systematically reviewed the drug therapy for paediatric LCOS – for a single drug (Supplement A).

The web-based distribution of a questionnaire is a method that was used to quantify drug use for paediatric LCOS across Europe via EuLoCOS-Paed providing the information for objective decision-making. It gives a close-to complete list of drug use. To prioritise research needs independent of their labelling status and putative evidence on their safety and efficacy closes the gap between the paediatric needs and priority list by the EMA. It also provides an unbiased presentation of those drugs, which are "likely to generate the most interest for the greatest number of centers" in line with the Cardiology Group on Postoperative Cardiac Dysfunction [10].

Revealing off-label facets in approved drugs

Albeit prescribed off-label at the time of survey conduct, milrinone has been approved for the treatment of paediatric LCOS in 2011/2012 across Europe based on the conclusion of the European Public Assessment Report in accordance with Article 45 of the Paediatric Regulation and through the European paediatric work sharing procedure [3]. Thus, further studies on the safety and efficacy of milrinone in paediatric LCOS, including PBPK drug-disease modelling and simulation for milrinone, could be considered redundant. However, off-label facets can be identified in the SmPC of milrinone [11] that hamper the proper use of milrinone for paediatric LCOS and demand further pharmacokinetic research investigations.

Firstly, milrinone's upper dose range for the loading and maintenance infusion as well as the duration of drug administration is taken from a clinical trial on paediatric LCOS prevention [11, 12] but proven safety and efficacy of milrinone for LCOS prevention cannot necessarily delineated for LCOS treatment. Secondly, the SmPC advises to consider the results from existing pharmacokinetic studies for dose selection in paediatrics due to the known effect of age on drug exposure. However, a general statement that optimal dosing seems to be higher in paediatric than in adult patients while preterm newborns may need a lower dose than children is insufficient in clinical practice if a factor 3 dose range is provided for the maintenance infusion. Thirdly, milrinone is contraindicated in paediatric patients with renal impairment although they constitute the majority of patients with LCOS after open heart surgery [13]. Lastly, the pharmacokinetic parameters and respective values provided in the pharmacokinetic property section of the SmPC present a mix of paediatric data from different indications, pharmacokinetic analysis methods and age groups. As no further explanation of the paediatric studies is provided, it is impossible to accurately interpret, judge and utilise the information for dose-selection in view of the licensed indication – paediatric LCOS treatment.

Table 1 Comparison of the Summary of Product Characteristics entries with the original study data for milrinone

Milrinone SmPC extract [11]		**Characteristics of implemented studies in the milrinone SmPC**				
Age group (ICH classification)	Milrinone clearance	Milrinone clearance CV (%)	Age (N)	Indication	PK analysis	Reference
Children (2-11 years)	5.9-6.7	5.9 (34)	1-13 y (N=7)	Postoperative inotropic support	NCA	[14]
		6.7 (-)	2-6 y (N=12)	LCOS prevention	CA	[15]
Infants (28^{th} day to 23 months)	3.4-3.8	3.4 (67)	1-24 months (N=94)	LCOS prevention	CA	[15]
		3.8 (26)	1-9 months (N=12)	Postoperative inotropic support	NCA	[14]
Neonates (0-27 days)	1.64	1.64 (157)	0-1 month (N=48)	LCOS prevention	CA	[15]
Preterm infants	0.64	0.64 (24)	Born before 29 weeks of gestation (N=29)	Prevention of low systemic blood flow	CA	[16]

Units and abbreviations: Milrinone clearance in ml/min per kg bodyweight; SmPC, Summary of Product Characteristics; ICH classification, paediatric age classification as developed by the International Conference on Harmonization (ICH) and shown in [17]; CV, coefficient of variation; PK analysis, type of pharmacokinetic analysis undertaken in the studies; NCA, noncompartmental analysis; CA, compartmental analysis; LCOS, low cardiac output syndrome.

The discrepancies are not surprising given the fact that the Medicines and Healthcare products Regulatory Agency in the UK previously concluded that the "kinetics of milrinone are not established in children and infants" [18] and the EMA stressed the priority need for data on milrinone's pharmacokinetics, efficacy and safety for use in cardiac failure [8]. In fact, no new pharmacokinetic data on milrinone in paediatric LCOS became available since the conclusions of the regulatory authorities and the judgement of milrinone's pharmacokinetics and licensing status in the European Public Assessment Report [3] was consequently based on the same level of literature. In addition,

milrinone for paediatric LCOS prevention continues to be subject to off-label prescribing with insufficient dose guidance being available.

Maximising gain of knowledge from existing information while minimising patients' risk

In contrast to other drugs for paediatric LCOS, the pharmacokinetics of milrinone have been explored in preterms, neonates, infants and children highlighting that total plasma clearance of milrinone differs across the paediatric age groups [14, 15, 19, 20]. This is fundamental knowledge that should influence dosing. However, the exact link between age and exposure is difficult to extract from these data, for example due to the clustering of wide age groups. Clearance prediction equations for milrinone have also failed clinical practice evaluation [21]. Thus, it seemed only logical to make best use of the existing pharmacokinetic data by integrating them into a novel modelling and simulation approach and circumventing the constraints of previous pharmacokinetics studies with milrinone in paediatric patients.

The novel approach presented in *Chapter 4* embraced whole-body PBPK modelling and simulation, an *in-silico* technique that has been shown to adequately describe drug exposure in neonates, infants and children especially due to the work by Edginton et al. [22], Björkman [23] and Johnson et al. [24]. In previous publications, drug clearance was scaled by probably assuming a negligible effect of disease on drug exposure, which may be applicable to some diseases. However, this is not true for LCOS and open heart surgery, which impact drug exposure by altering protein and haematocrit levels, inducing volume overload, reducing cardiac index, re-distributing blood flow, and decreasing metabolism and elimination capacities [25]. Milrinone clearance scaling from healthy adults to paediatric patients with LCOS after open heart surgery would, therefore, be inadequate. Also, milrinone clearance scaling from adult patients with LCOS after open heart surgery would provide misleading results due to significant differences in disease etiology [26], comorbidities [27] and impact of surgery between adult and paediatric patients [25] but also the normal age-related decline of organ function in adult patients with advanced age [28]. Consequently, a disease model needed to be developed that could bridge the disease and age-related differences among healthy young adult volunteers, adult patients and paediatric patients with and without LCOS after open heart surgery, and that disease model needed to be coupled with the PBPK drug model for milrinone.

Previous work in adult patients with liver [29, 30] and renal disease [31] or undergoing non-cardiac surgery [32] demonstrated the usefulness of a combined PBPK drug-disease model to assign the influence of disease versus no-disease on drug exposure. This ground-breaking knowledge on disease modelling was integrated into this research but it needed to be extended to the indication of LCOS with the external appliance of cardiopulmonary bypass and to paediatric patients. The development and full performance evaluation of the PBPK drug-disease model was verified with historical data given the richness of pharmacokinetic studies on milrinone established over the last 30 years in healthy adult volunteers [33, 34], adult [35–38] and paediatric patients [14, 15, 20] with and

without LCOS after open heart surgery and adult patients with congestive heart failure [39]. Thus, the gain of knowledge from already existing information was maximised while the risk of patients with regard to clinical trial participation was minimised.

Facing the limitations of historical data

The use of historical data, albeit recorded prospectively at the time of study conduct, embarks limitations and they need to be discussed to make an informed decision on the validity of their inclusion for model development and evaluation.

Firstly, most studies provided summary data for plasma concentrations or did not link individual plasma concentration time profiles with the respective patients. Also, another study [15] involved a sparse sampling scheme with a maximum of two blood samples drawn from each patient, which provides limited informative value for an individualised patient pharmacokinetic analysis. Therefore, a population-based PBPK analysis was employed in *Chapter 4* to circumvent the limitation of unknown parameter values and make use of the existing summarised historical data. Population pharmacokinetic analysis also enables the exploration of covariates to explain inter- and intraindividual variability [40], which becomes especially valuable when designing dosing algorithms for an entire patient population as endeavoured in this research.

In addition to the insufficient description of blood sampling techniques as described in *Chapter 4*, the non-standardised assessment of LCOS provided another limitation, which required an assignment of patients to those with or without LCOS based on surrogate characteristics. In that respect, patients in need for postoperative inotropic support and/or with a reported cardiac index of less than 2-2.2 l/min per m^2 were considered with LCOS [41, 42] and haemodynamically stable patients and not in need for postoperative inotropic support but with a cardiac index less than 3 l/min per m^2 were considered without LCOS [35, 36]. This made a distinct assignment of the pharmacokinetic studies possible using the same algorithm. Nonetheless, it shall not hide the fact that there is a lack of a uniform definition for LCOS that needs to be endeavoured to allow outcome comparability between studies and drugs.

Lastly, the inclusion of different pharmacokinetic studies also embarks the risk of inter-laboratory and inter-assay variability, which may question the accurateness and reliability of the measured milrinone plasma samples and limit a joined analysis. However, the fact that milrinone plasma concentrations were determined at a single centre for each study with previously validated assays underscores their usefulness. Seven studies adopted the milrinone assay developed by Edelson et al. [43], which includes a stepwise double-liquid extraction, evaporation, back-extraction, evaporation, pH neutralisation and subsequent separation and quantification via high pressure liquid chromatography and ultraviolet detection. Two other studies reported a modified version of the former by simplifying the initial extraction procedure [44, 45] and one study used an assay that was previously validated for the determination of amrinone's plasma concentrations for which milrinone

was used as the internal standard [46]. Herein, a precipitation step was followed by solid phase extraction. In all, the reported assays used authenticated analytical reference standards and the values for accuracy and precision (1.3-15%) were within the recommended limits set by the U.S. Food and Drug Administration (FDA) for bioanalytical method validation [47]. This supported their use for a joined pharmacokinetic analysis.

Developing and evaluating PBPK models

Although the integration of PBPK drug-disease modelling into paediatric drug development proposals is strongly encouraged by the EMA [48], the approach is still in its infancy and explicit guidance on the development and evaluation of these models has not been yet established by regulatory authorities. Nonetheless, viewpoints on best practice on the general use of PBPK modelling and simulation [49] and the workflow for paediatric PBPK model development and verification [50] are published by regulatory assessors. Workflows from previously published adult PBPK drug-disease models [29, 30, 51] are also available, which are comparable to the PBPK model flow to explore drug-drug interaction potentials between two drugs as provided in the draft guidance by the FDA [52]. Furthermore, the World Health Organization published guidance on the use of PBPK modelling in risk assessment [53], which provides valuable information on the evaluation of PBPK models. For this research, the existing knowledge was merged and tailored to paediatric PBPK drug-disease modelling to provide grounds for a rationale model development and evaluation.

As requested by regulatory assessors, an open and clear description of all information on input parameters was provided in *Chapter 4* to comprehend step-wise modelling and simulation [49]. In addition, the FDA advises the assessment of predictive model performance if the model is used for the recommendation of new dosing algorithms [40] as is the case in the research here presented. This was not only done by using the same data set (internal validation) as applied for building the adult PBPK model for milrinone, but also by using 10 different data sets (external validation) that were not applied for model building. The rigorous external validation is a real strength of this research as it is most stringent in terms of assessing model adequacy. It provides information on the wider application of the model to different subpopulations and ethnicities, disease states and dosing regimens in contrast to internal validation techniques [54].

LESSONS LEARNED FROM EULOCOS-PAED

EuLoCOS-Paed provides quantitative data on drug use for paediatric LCOS after open heart surgery. The lessons learned refer to the level of off-label and variability of drug use, differences between LCOS prevention and treatment but also between adult and paediatric patients, substantial gaps in targeted research and the sources of information currently available for safe and effective prescribing of drugs. This knowledge is pivotal to allow an objective and reliable assessment of drug therapy, the

identification of paediatric needs and a targeted approach towards future clinical research and healthcare expenditures with the overall aim to improve the standard of care for paediatric patients with open heart surgery.

Lesson 1 - Off-label drug use is nearly absolute.

EuLoCOS-Paed revealed a 97% off-label drug use for the treatment of paediatric LCOS at the time of survey conduct, which is slightly higher than the 92% previously reported by Pasquali et al. [55] for paediatric patients with congenital heart disease undergoing surgical procedure. Nonetheless, it also confirms Pasquali's findings that off-label drug use is highest in the youngest and most severely ill patients and directly reflects the life-threatening clinical scenario of LCOS after open heart surgery that predominantly affects neonates and infants.

Lesson 2 – Drug treatment for paediatric LCOS is highly variable.

The clinical scenario LCOS with elevated systemic vascular resistance shall exemplify the identified variability in the European practice pattern, for which 32 different drug regimens were reported for the initial treatment step and in total, 23 different drugs from eight therapeutic drug classes for the initial and two add-on treatment steps. Variability itself may not be surprising given the little published evidence and guidance available in this field. However, the magnitude of different drugs and drug combinations from various therapeutic drug classes was unexpected and seemingly higher than in adult patients with LCOS [56–58].

Lesson 3 - LCOS is not a uniform entity.

The survey results demonstrated that treatment differs for each LCOS subtype and for the first time, treatment algorithms are presented for the initial treatment step and two subsequent add-on steps for LCOS with elevated and low systemic vascular resistance as well as elevated pulmonary vascular resistance. Albeit four drugs, namely milrinone, dobutamine, dopamine and epinephrine, were reported for all LCOS subtypes, drug use was also subtype specific. For example, vasopressin was only reported for LCOS with low systemic vascular resistance; inhaled nitric oxide, sildenafil and prostacyclin derivatives were reported solely for LCOS with elevated pulmonary vascular resistance. This knowledge contributes to a more complete understanding of paediatric LCOS treatment.

Lesson 4 – There are substantial gaps in targeted drug research.

The comparison between the 13 most commonly reported drugs for paediatric LCOS in EuLoCOS-Paed and the drugs listed in the draft "Inventory of paediatric needs: Cardiovascular therapeutic area" by the EMA [9] shows that eight out of the 13 drugs are actually listed for intensified research and development but only two drugs, namely vasopressin and dobutamine, are particularly listed for the indication cardiogenic shock or acute heart failure. In addition, four commonly reported drugs in

EuLoCOS-Paed, i.e. enoximone, glyceryl trinitrate, prostacyclin derivatives and epinephrine, are not listed in the draft inventory by the EMA despite the lack of an approved indication.

Lesson 5 –Paediatric LCOS prevention is common clinical practice that goes unnoticed.
For the first time, EuLoCOS-Paed disclosed the urgency for more attention and research on paediatric LCOS prevention by showing that it has become an integrated part of the perioperative management for paediatric patients with open heart surgery. However, European hospital practice pattern is highly variable with regard to patient and drug selection, as well as dosing and timing of drug administration. Although milrinone is reported the drug of choice, which is in line with the available evidence [12], the reported dosing algorithms do not match the evidence. In all, drug use is completely off-label and the draft "Inventory of paediatric needs: Cardiovascular therapeutic area" [9] does not address this topic.

Lesson 6 – Four drugs assemble the candidate list for prioritised drug research.
The results of EuLoCOS-Paed demonstrated that milrinone, epinephrine, dopamine and dobutamine are the mostly reported drugs for the treatment of paediatric LCOS and should be targeted for future research. In addition, the four drugs are also commonly used for LCOS prevention together with levosimendan albeit milrinone clearly is the drug of choice for this indication.

Lesson 7 – Prescribing for paediatric LCOS is limited by the lack of guidance – to many clinicians.
EuLoCOS-Paed enabled clinicians to express their views on the availability of drug and dosing information for prescribing. This was stated insufficient by 40% of the respondents; 88% of the respondents favoured the availability of clinical practice guidelines in this field. Of course, the results are specific for paediatric LCOS but they also underpin the general lack of sufficient prescribing support in paediatrics as previously highlighted by Barrett et al. [59]. Nonetheless, it shall not be left unnoticed that 57% of the EuLoCOS-Paed survey participants actually believed that currently available drug and dosing information is sufficient to prescribe for paediatric patients with LCOS after open heart surgery.

IMPLICATIONS FROM EULOCOS-PAED

The Institute of Medicine stated that "patients should receive care based on the best available scientific knowledge and care should not vary illogically from clinician to clinician or from place to place" to improve the quality of health care [60]. In contrast, EuLoCOS-Paed identified a highly variable practice pattern for paediatric LCOS among European hospitals driven by the lack of evidence, approved drugs and prescribing guidance, which is expected to result in suboptimal LCOS treatment and prevention in paediatric patients. Consequently, there is a definite need for more

research to ensure safe and effective drug therapy for paediatric patients with open heart surgery towards improving the quality of health care. This also requires a focus change on LCOS prevention, which has been previously left unattended by regulatory authorities. The aim should be to come to a consensus on a specific definition for LCOS (to know what to treat), define the patient group that is likely to benefit from drug therapy (to know who to treat), and establish safety, efficacy and pharmacokinetic data for the drugs used for paediatric LCOS (to know how to treat) as discussed in *Chapter 3*.

First of all, public awareness of the identified issues in EuLoCOS-Paed needs to be raised among clinicians and other healthcare provider but also regulatory authorities. Clearly, off-label use of drugs in paediatric cardiac intensive care is common practice and without it, patients would be denied essential drug treatment in an acute, life-threatening clinical situation, such as LCOS [55]. The problem, however, arises when drug use cannot be supported by strong evidence for its safety and efficacy as it happens for the highly variable prescribing pattern for paediatric LCOS treatment and prevention across Europe. In this case, clinical experience becomes mandatory in daily hospital practice but must be seriously scrutinized for its good and bad towards patient outcome. Therefore, the results of EuLoCOS-Paed were disseminated to the survey participants and published in journals dedicated to the care of paediatric patients to increase awareness and trigger an open discussion. The results were also integrated into the EMA draft consultation on the "Inventory of paediatric needs: Cardiovascular therapeutic area" in October 2012 to highlight substantial gaps in targeted drug research. In consequence, the inventory of paediatric needs has been extended for levosimendan and nitroprusside to also address dose, safety and efficacy data for paediatric LCOS treatment and prevention. Furthermore, epinephrine and prostacyclin derivatives have been newly added to the inventory and the case has been reopened for dopamine especially for paediatric LCOS (Supplement C).

Equally important is the commitment to paediatric cardiovascular research by healthcare providers and parental guardians [61]. More than 50% of the EuLoCOS-Paed survey participants are satisfied with the level of drug and dosing information, which raises the question on which trustworthy basis they safely and effectively prescribe for paediatric patients. The level of evidence for the drug of choice, dobutamine, in guidelines is graded not more than low as shown in *Chapter 2*; even the EMA [8] and the U.S. FDA [62] demand more extensive studies on dopamine and dobutamine to ensure proper use in paediatric patients. So why do healthcare providers do not collectively stand up if they have the chance to make a change? This seems to be a fundamental question that has been also highlighted in previous research. McLay et al. [63] showed that 37% of Scottish hospital based paediatricians did not believe new medicines should be trialled in children; 63% of the surveyed paediatricians felt the same about off-patent medicines. The study was conducted between 2003 and

2004 but similar numbers have been shown by Mukattash et al. [64] in 2008 for Irish paediatricians. To give another two examples, only 15% and 50% of paediatricians specialised in intensive care have concerns regarding the efficacy and safety of off-label prescribing, respectively [65]; 92% of consultant paediatricians do not believe that licensing more medicine for paediatric use would reduce the dosing error rate [64]. In addition, the majority of paediatricians do not inform parents about off-label prescribing for their child, but to inform parents on off-label drug use has been shown to be pivotal to increase parents' acceptance of paediatric clinical trials [66]. Therefore, the next stage of research also needs to explore the reasons for paediatricians' "less than wholehearted acceptance of the need for such studies" [63] as they are a key for successful study recruitment.

Making use of existing networks of specialists in the field, such as the one established for EuLoCOS-Paed, can subsequently result in agreements on consensus definitions for LCOS or risk stratification schemes of patients for receiving LCOS prevention. The successful international paediatric sepsis consensus definition on shock using focus groups [67] or the definition on "off-label use of drugs" using the Delphi method by Neubert et al. [68] exemplify the feasibility and encourage transferability to paediatric LCOS. This should be the basis for any future endeavours of paediatric cardiovascular trials.

EuLoCOS-Paed provides the means to prioritise the critical evaluation of drugs towards a targeted approach to future clinical research and utilisation of healthcare resources. To overcome the many challenges towards successful paediatric cardiovascular research and to avoid failure, however, the lessons learned from previous cardiovascular drug trials have to be implemented, such as the inevitable understanding of the nature of disease in the paediatric patient group of interest [69]. The formal evaluation of the pharmacokinetics and pharmacodynamics of drugs and implementation into clinical trial planning as well as a valid selection of clinical endpoints has been regarded equally important for successful trial outcome [69]. Again, networking of collaborative clinical trial centres is essential to establish the grounds for well-powered drug trials given the small sample size and disease heterogeneity [10].

Innovative study designs for paediatric drug trials have to be applied to minimise trial-related risks and maximise the benefits for current and future patient populations. Alternative trial designs can tackle methodological (sample size) and ethical barriers (placebo control group) of randomised clinical trials, which have been so far considered the gold standard for the assessment of drug safety and efficacy [70]. Alternatives are presented by using adaptive and Bayesian designs [70] but also by integrating modelling and simulation to design more informative clinical trials in paediatric patients [71]. Modelling and simulation offer the main benefits of compiling data from different sources and driving interferences to minimise the number of participants in trials in accordance with Manolis et al.

[72]. Therefore, an implication of EuLoCOS-Paed was also to embrace milrinone with novel PBPK drug-disease modelling and simulation in this thesis to evaluate and optimise current dosing algorithms but also to provide age-appropriate optimised dosing strategies that clinicians can opt for the drug with potential of contributing to safer and more effective drug therapy for paediatric LCOS.

At last, the evidence on the safety and efficacy of drugs and/or drug combinations for paediatric LCOS needs to be compiled, assessed and graded, which should ultimately result in clinical practice guidelines as demanded by the EuLoCOS-Paed survey participants. The next step is then to implement the research findings into clinical practice by ensuring dissemination and education that benefit clinicians and patients towards an improved postoperative patient care [61]. Use of drugs and outcome should be recorded, for example, by extending available databases, and subsequently analysed. The clear benefits of implementing guidelines have been shown for the management of paediatric and neonatal shock by demonstrating a significant reduction in morbidity and mortality [73], which should be equally endeavoured for paediatric patients with open heart surgery.

LESSONS LEARNED FROM PBPK DRUG-DISEASE MODELLING & SIMULATION

The development and application of the novel paediatric PBPK drug-disease model for milrinone in patients with and without LCOS after open heart surgery provided knowledge on two different levels. Firstly, lessons were learned about the influence of disease and age on milrinone exposure. This way, PBPK modelling and simulation complements existing knowledge on the pharmacokinetics of milrinone. In a wider perspective, the specific example also provides essential knowledge on the feasibility and transferability of paediatric PBPK drug-disease modelling in general, which is still in its infancy with little available evidence on the capabilities as an exploratory tool for improving drug dosing.

Lesson 1 – Milrinone plasma clearance shows a non-linear dependence on paediatric age.
Retrograde scaling of milrinone's clearance from adults to paediatrics demonstrated a non-linear change in steady-state plasma concentration, and therefore, clearance of milrinone with age in the PBPK model. Like this, drug exposure is predicted highest in neonates, followed by patients aged 1-12 months and 9-15 years, and exposure is lowest in patients aged 1-9 years for a given maintenance infusion dose. This finding challenges previous pharmacokinetic analyses of milrinone in paediatric patients aged 0-6 years describing a linear age-dependency of milrinone's total plasma clearance [15, 20], but which failed clinical practice evaluation [21]. In contrast, the non-linear dependence of milrinone clearance on age reflects a system-biology based approach considering growth and maturation for the description of milrinone pharmacokinetics [74].

Lesson 2 – Milrinone pharmacokinetics differs between old and young as well as disease states.
The coupled PBPK drug-disease model provided the means to learn about the similarities and differences between adult and paediatric patients with and without LCOS after open heart surgery with regard to milrinone exposure. It showed that the postoperative impact of disease due to LCOS and surgery is similar between adult and paediatric patients after adjusting for the normal age-related decline in organ function. However, pre-operative organ function is much more impaired in adult than paediatric patients who develop LCOS after open heart surgery. In addition, the impact of pre- and postoperative organ function on drug exposure significantly differs between patients with and without LCOS and this is mainly driven by renal and hepatic function, organ blood flows, haematocrit and plasma albumin abundance.

Lesson 3 – Recommended doses do not provide adequate milrinone exposure for all patient groups.
The evaluation of milrinone prescribing guidance for LCOS treatment in paediatric patients indicated that the recommended maintenance infusion of 0.25-0.75 µg/min per kg from the SmPC [11] may provide adequate exposure for all paediatric age groups if guidance existed on how to apply the dose range to paediatric patients of different age groups. However, this guidance does not exist and blind dosing may ultimately result in supra- and subtherapeutic levels. This equally applies to the recommended loading dose of 50-75 µg/kg over 30-60 min [11]. Dosing for paediatric LCOS prevention in accordance with the evidence from PRIMACORP [12] and EuLoCOS-Paed (*Chapter 2* and *3*) would also not be capable of providing the recommended therapeutic target range across all paediatric age groups [3]. A maintenance infusion without prior loading may even delay the timely required therapeutic plasma concentrations, thus loosing valuable time for LCOS prevention. In adults, supratherapeutic plasma levels of milrinone are predicted for patients with and without LCOS with current loading doses while approximately 25% of the patients are predicted to have supra- and subtherapeutic steady-state plasma concentrations with the maintenance infusion doses [11, 36].

Lesson 4 –Renal and hepatic impairment can affect milrinone exposure.
Renal impairment necessitates dosing adjustment for milrinone and respective algorithms were presented for adult patients in the SmPC [11]. The integration of a regulator component into the PBPK model for milrinone to quantify the effect of renal function on milrinone's fraction excreted unchanged in urine, however, also let us learn about the increasing importance of hepatic function with declining renal function. Given a nearly 30 ml/min per 1.72 m^2 glomerular filtration rate in adult patients with LCOS after open heart surgery [75], 40% of milrinone is predicted to be hepatically metabolised versus 18% in healthy young adults. Thus, metabolism and excretion may depend more on hepatic function than previously anticipated.

Lesson 5 – Successful collaboration between academia and industry minimises patient's risk.
Chapter 4 presents a process flow for model development and evaluation that provides an example on how to make best use of existing historical data by re-analysing them using a different technique. Like this, the costs, time, ethical barriers and risks associated with the conduct of a clinical trial to obtain milrinone plasma samples were circumvented, which equally benefited patients and research. This was feasible by directly involving the marketing holder in the project given a successful project proposal submission that allowed timely access to crucial data for model development [33] and paediatric model evaluation [15]. In addition, researchers from the US [20, 35], UK [45], and Japan [38] were attracted to share their data.

Lesson 6 – Paediatric PBPK drug-disease modelling is feasible but depends on data integrity.
The herein presented PBPK drug-disease model lets us learn about the feasibility and transferability of disease modelling from adults to paediatrics, particularly for a condition that shows marked pathophysiological differences between old and young. The workflow comprised a stepwise approach from healthy adult volunteers scaled to paediatrics as recommended by regulatory assessors [50] with an intercalated disease model development step from adults to paediatrics that complements existing workflows for PBPK modelling. Intercalation is necessary because pharmacokinetic data in paediatric patients are reflective of disease; simple clearance scaling from healthy young adults to paediatrics overlooks this precise difference between the populations but needs to be considered when disease alters absorption, distribution, metabolism and/or excretion. Furthermore, disease modelling highlighted the need for separating the age-related influence on clearance deterioration from the impact of disease in adult patients of advanced age to transfer disease-related factorial changes of organ function to paediatrics as described in *Chapter 4*. In all, several paediatric PBPK drug models have been successfully established so far but the link to disease has not been fully integrated yet [22–24]. *Chapter 4* fills this gap of knowledge to some extent. However, model development also made aware of deficits in clinical research, especially in paediatrics.

IMPLICATIONS FROM PBPK DRUG-DISEASE MODELLING & SIMULATION

Understanding the pharmacokinetics and pharmacodynamics of milrinone in paediatrics as well as the impact of disease on the distribution, metabolism and excretion of milrinone is key for safe and effective prescribing. Clinical practice reflection, however, indicates that this is insufficiently met and there is a dire need for improvement. In fact, EuLoCOS-Paed showed that prescribing for milrinone in paediatric patients for LCOS treatment and prevention is highly variable, which often results in supra- and subtherapeutic plasma levels and exposes paediatric patients to adverse drug effects or treatment failure [21]. Clinicians also neglect milrinone dose adjustments in paediatric patients with compromised renal function albeit strongly recommended in adult patients [76]. A core element,

however, towards safe and effective prescribing for milrinone is missing, namely adequate guidance. Thus, the lessons learned from PBPK drug-disease modelling have important implications for future milrinone prescribing and shall equally encourage the adaptation of paediatric PBPK drug-disease modelling to address other labelling deficits in near future.

Of outmost importance, current prescribing for milrinone needs to be challenged and looked at from a new perspective. Lessons 1 to 3 learned from PBPK modelling clearly implicate that one dose cannot fit all – neither for paediatric patients across different age groups nor for adult and paediatric patients and lastly, neither for those patients requiring milrinone for LCOS prevention and LCOS treatment. Firstly, dosing in paediatric patients needs to be age-stratified to ensure comparable drug exposure across the entire paediatric age groups. Secondly, paediatric patients with LCOS after open heart surgery require lower maintenance infusion doses than haemodynamically stabilised patients of similar age. Thirdly, optimised dosing for LCOS treatment and prevention differs between adult and paediatric patients and precludes dose scaling attempts.

Ongoing research needs to be endeavoured. Although the predictive performance of the PBPK drug-disease model for milrinone in patients with and without LCOS was assessed following the recommendations by the U.S. FDA [40], a prospective clinical practice evaluation is recommended to finally show the usefulness and applicability of the herein presented model. This can be done within a therapeutic drug monitoring programme as suggested for adult patients with advanced heart failure [77] or a prospective clinical trial using a random milrinone plasma sampling scheme and a statistically pre-quantified number of paediatric patients per age group for hypothesis testing. This data would also allow the verification of dosing regimens for children aged 6 years and older with little confirmatory data available during model evaluation.

In addition, research on milrinone needs to disclose the underlying pharmacokinetic principles to fully understand the influence of patient's renal and hepatic impairment on drug exposure and allow subsequent dose adjustment. As shown by Woolfrey et al. [45] and integrated into the present PBPK model, patients with moderate and severe renal impairment metabolise and excrete milrinone differently from healthy adults. The fraction of milrinone excreted unchanged into urine decreases and the increased non-renal clearance has been attributed to milrinone's hepatic metabolism based on similarities to the metabolism of furosemide [45]. Nonetheless, the formal proof is missing as does the information, which exact enzymatic processes govern milrinone glucuronidation. On a wider perspective, research also needs to fill the gaps of knowledge with regard to human pharmacology, physiology and our understanding of growth and maturation of organ function. These gaps currently set the limits to complete system-biology based modelling and simulation. Upon availability of the

new data, they can be readily integrated into the PBPK drug-disease model given the flexibility of the system-biology approach.

Furthermore, the study demonstrates the potential use of PBPK drug-disease modelling and simulation to optimise dosing strategies for paediatric patients, and shall encourage its future adaptation to address other paediatric drug labelling deficits, which is in keeping with the view of regulatory authorities [48]. The PBPK drug-disease model for milrinone in patients with open heart surgery itself presents two more options for elaboration, namely on the drug level and on the disease level given the independent nature of the model components. The first option provides the opportunity to learn about the pharmacokinetic profile of other drugs commonly reported for paediatric LCOS in EuLoCOS-Paed for which further research is necessary. Levosimendan is especially interesting because both the parent drug and the active metabolite are responsible for drug action and there may be polymorphically differences in drug metabolism [78]. Thus, a coupled PBPK drug model for levosimendan can be built, which considers pharmacokinetic, pharmacogenetic and pharmacodynamic differences among the patient populations. The second option, elaborating on the disease level, provides the opportunity to learn about the pharmacokinetic profile of milrinone in patients with different diseases. This is important because one drug may not only be used for one indication as it happens with milrinone. Other paediatric off-label indications of milrinone with insufficient pharmacokinetic knowledge include the treatment of persistent pulmonary hypertension of the newborn [79] and bridging to transplantation in paediatric patients with advanced heart failure [80]. Thus, PBPK drug-disease modelling and simulation can substantially contribute to a better understanding of drug exposure for different disease states and ultimately support the extension of therapeutic drug label indications.

At last, data sharing should be endeavoured whenever possible to avoid unnecessary trials and speed up clinical practice research to benefit and most importantly, value the patient [81]. From a small scale perspective, the feasibility of data sharing between industry and academia has been successfully demonstrated in this thesis, which resulted in optimised dosing strategies for a single drug and a given disease. But data sharing should encompass more than the original pharmacokinetic data sets and involve a wider audience to make best use of available data, expert knowledge and experience. The ultimate aim, to develop evidence-based dosing algorithms for as many drugs and indications as possible, cannot be achieved by a single researcher and data transfer circumvents re-inventing the wheel if previous models can be the backbone of future work. The Drug Disease Model Resources project, short DDMoRe (www.ddmore.eu), sets an example of developing a public drug and disease model repository, which is supported by a European Union and pharmaceutical industry partnership. Although at the initial development steps, the leading idea of DDMoRe is to facilitate knowledge integration for decision-making by establishing and providing public access to an open source

interoperability framework of drug and disease models. Patient-centred care may also evolve by developing user-friendly computer interfaces for bedside drug-disease simulation. This would bring research right to the patient and would allow timely integration of clinical and patient specific parameters for decision-making. The dashboards for methotrexate and tacrolimus within the Pediatric Knowledge Base developed by the Children's Hospital of Philadelphia, US, are such an example based on nonlinear mixed effect modelling techniques (http://pkb.chop.edu/dashboards). The ultimate aim, however, should be to extend these databases to also include PBPK modelling and simulation work to complement existing modelling techniques. The idea follows the altruistic principles of improving our understanding of drugs and the interaction with disease as well as concomitant medication towards benefiting patient care. This requires the ambitious support by researchers, industry, funding bodies and patients or parental guardians.

CONCLUSION

In conclusion, this thesis has presented an integrated research approach to optimise dosing strategies of drugs for the treatment and prevention of paediatric LCOS by first revealing the prescribing pattern of drugs for LCOS in paediatric patients after open heart surgery across Europe, and then by developing a novel model-based approach to embrace the developmental changes across the paediatric life stages, the effects of disease and open heart surgery on drug exposure. The questionnaire survey EuLoCOS-Paed provides the grounds for an objective and systematic paediatric needs assessment and highlights substantial gaps in European governed research. Consequently, the integration of the results into the "Inventory of paediatric medicines: Cardiovascular therapeutic area" by the EMA are hoped to positively impact future drug research and development, which shall provide answers to the currently existing questions on paediatric LCOS prescribing. The novel population based PBPK drug-disease model addresses these questions from EuLoCOS-Paed by evaluating and optimising current dosing strategies for paediatric LCOS and clinicians' drug of choice for this indication – milrinone. At the same time, the herein presented research demonstrates the feasibility and transferability of paediatric PBPK drug-disease modelling and simulation, and provides the proof-of-concept of its capabilities as an exploratory tool for improving paediatric drug dosing.

REFERENCES

1 Meyer S, Abdul-Khaliq H, Gortner L. The use of milrinone in pediatric intensive care medicine. *Paediatr Anaesth* 2012;22(2):182–183.

2 van Saet A, de Wildt SN. Prevention of Low Cardiac Output Syndrome in children: where is the evidence? *Paediatr Anaesth* 2011;21(12):1173–1175.

3 European Medicines Agency. Milrinone: Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended 2011. http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Paediatric_Regulation/Assessment_Reports/Article_45_work-sharing/Milrinone-_2011_06_Art.45PaedPdAR.pdf. Accessed 11 Mar 2013.

4 Nieminen MS, Brutsaert D, Dickstein K, *et al.* EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;27(22):2725–2736.

5 Ricci Z, Garisto C, Favia I, *et al.* Levosimendan infusion in newborns after corrective surgery for congenital heart disease: randomized controlled trial. *Intensive Care Med* 2012;38(7):1198–1204.

6 Lechner E, Hofer A, Leitner-Peneder G, *et al.* Levosimendan versus milrinone in neonates and infants after corrective open-heart surgery: a pilot study. *Pediatr Crit Care Med* 2012;13(5):542–548.

7 Fresenius Kabi Deutschland. Summary of Product Characteristics for Dobutamin Liquid Fresenius 250 mg/50 ml Infusionslösung (INN: Dobutamine) 2008. http://www.fachinfo.de. Accessed 1 Jul 2013.

8 European Medicines Agency. Revised priority list for studies into off-patent paediatric medicinal products for the Fifth Call 2011 of the 7th Framework Programme of the European Commission, Rev. 2010 (Doc. Ref.: EMA/253396/2010).

9 European Medicines Agency. Inventory of paediatric medicines: Cardiovascular therapeutic area (EMA/550070/2012) 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/08/WC500131636.pdf. Accessed 11 Mar 2013.

10 Roth SJ, Adatia I, Pearson GD, *et al.* Summary proceedings from the cardiology group on postoperative cardiac dysfunction. *Pediatrics* 2006;117(3 Pt 2):S40-6.

11 Sanofi Aventis. Summary of Product Characteristics for Primacor 1mg/ml Solution for Injection (INN: Milrinone) 2011. http://www.medicines.org.uk/EMC/medicine/6984/SPC/Primacor+1mg+ml+Solution+for+Injection/. Accessed 1 Jul 2013.

12 Hoffman TM, Wernovsky G, Atz AM, *et al.* Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation* 2003;107(7):996–1002.

13 Zappitelli M, Bernier P, Saczkowski RS, *et al.* A small post-operative rise in serum creatinine predicts acute kidney injury in children undergoing cardiac surgery. *Kidney Int* 2009;76(8):885–892.

14 Ramamoorthy C, Anderson GD, Williams GD, *et al.* Pharmacokinetics and side effects of milrinone in infants and children after open heart surgery. *Anesth Analg* 1998;86(2):283–289.

15 Bailey JM, Hoffman TM, Wessel DL, *et al.* A population pharmacokinetic analysis of milrinone in pediatric patients after cardiac surgery. *J Pharmacokinet Pharmacodyn* 2004;31(1):43–59.

16 Paradisis M, Jiang X, McLachlan AJ, *et al.* Population pharmacokinetics and dosing regimen design of milrinone in preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 2007;92(3):F204-9.

17 European Medicines Agency. ICH Topic E 11 - Clinical investigation of medicinal products in the paediatric population: Note for guidance on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99) 2001. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf. Accessed 17 Mar 2013.

18 Paediatric working group - Committee on safety of medicines. Review of paediatric data - Primacor Injecton 2005. http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con2030490.pdf. Accessed 1 Jul 2013.

19 Zuppa AF, Nicolson SC, Adamson PC, *et al.* Population pharmacokinetics of milrinone in neonates with hypoplastic left heart syndrome undergoing stage I reconstruction. *Anesth Analg* 2006;102(4):1062–1069.

20 Bailey JM, Miller BE, Lu W, *et al.* The pharmacokinetics of milrinone in pediatric patients after cardiac surgery. *Anesthesiology* 1999;90(4):1012–1018.

21 Garcia Guerra G, Senthilselvan A, Kutsogiannis DJ, *et al.* Safe administration of milrinone. *Pediatr Crit Care Med* 2011;12(3 (Suppl)):A11-A12.

22 Edginton AN, Schmitt W, Willmann S. Development and evaluation of a generic physiologically based pharmacokinetic model for children. *Clin Pharmacokinet* 2006;45(10):1013–1034.

23 Björkman S. Prediction of drug disposition in infants and children by means of physiologically based pharmacokinetic (PBPK) modelling: theophylline and midazolam as model drugs. *Br J Clin Pharmacol* 2005;59(6):691–704.

24 Johnson TN, Rostami-Hodjegan A, Tucker GT. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. *Clin Pharmacokinet* 2006;45(9):931–956.

25 van Saet A, de Wildt, SN, Knibbe, CAJ*, et al.* The Effect of Adult and Pediatric Cardiopulmonary Bypass on Pharmacokinetic and Pharmacodynamic Parameters. *Curr Clin Pharmacol* 2012 Dec 10. [Epub ahead of print].

26 Hsu DT, Pearson GD. Heart failure in children: part I: history, etiology, and pathophysiology. *Circ Heart Fail* 2009;2(1):63–70.

27 Webster G, Zhang J, Rosenthal D. Comparison of the epidemiology and co-morbidities of heart failure in the pediatric and adult populations: a retrospective, cross-sectional study. *BMC Cardiovasc Disord* 2006;6:23.

28 Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J Clin Invest* 1950;29(5):496–507.

29 Edginton AN, Willmann S. Physiology-based simulations of a pathological condition: prediction of pharmacokinetics in patients with liver cirrhosis. *Clin Pharmacokinet* 2008;47(11):743–752.

30 Johnson TN, Boussery K, Rowland-Yeo K*, et al.* A semi-mechanistic model to predict the effects of liver cirrhosis on drug clearance. *Clin Pharmacokinet* 2010;49(3):189–206.

31 Zhao P, Zhang L, Grillo JA*, et al.* Applications of physiologically based pharmacokinetic (PBPK) modeling and simulation during regulatory review. *Clin Pharmacol Ther* 2011;89(2):259–267.

32 Björkman S, Wada DR, Berling BM*, et al.* Prediction of the disposition of midazolam in surgical patients by a physiologically based pharmacokinetic model. *J Pharm Sci* 2001;90(9):1226–1241.

33 Stroshane RM, Koss RF, Biddlecome CE*, et al.* Oral and intravenous pharmacokinetics of milrinone in human volunteers. *J Pharm Sci* 1984;73(10):1438–1441.

34 Tsunoo M, Momomura S, Imai Y*, et al.* Safety, tolerance and pharmacokinetics of milrinone in phase I study in healhty male Japanese subjects (2) - After intravenous infusion. *Jpn Pharmacol Ther* 1993;21(12):201–221.

35 Butterworth JF, Hines RL, Royster RL*, et al.* A pharmacokinetic and pharmacodynamic evaluation of milrinone in adults undergoing cardiac surgery. *Anesth Analg* 1995;81(4):783–792.

36 Bailey JM, Levy JH, Kikura M*, et al.* Pharmacokinetics of intravenous milrinone in patients undergoing cardiac surgery. *Anesthesiology* 1994;81(3):616–622.

37 Das PA, Skoyles JR, Sherry KM*, et al.* Disposition of milrinone in patients after cardiac surgery. *Br J Anaesth* 1994;72(4):426–429.

38 Hasei M, Uchiyama A, Nishimura M*, et al.* Correlation between plasma milrinone concentration and renal function in patients with cardiac disease. *Acta Anaesthesiol Scand* 2008;52(7):991–996.

39 Benotti JR, Hood WB. Dose-ranging study of intravenous milrinone to determine efficacy and pharmacokinetics. In: Braunwald E, Ed. Milrinone: Investigation of new inotropic therapy for congestive heart failure. New York, NY: Raven Press 1984:95–107.

40 U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for industry - Population pharmacokinetics 1999.

http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133184.pdf. Accessed 17 Mar 2013.

41 Nieminen MS, Böhm M, Cowie MR, *et al.* Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005;26(4):384–416.

42 Rao V, Ivanov J, Weisel RD, *et al.* Predictors of low cardiac output syndrome after coronary artery bypass. *J Thorac Cardiovasc Surg* 1996;112(1):38–51.

43 Edelson J, Koss RF, Baker JF, *et al.* High-performance liquid chromatographic analysis of milrinone in plasma and urine. Intravenous pharmacokinetics in the dog. *J Chromatogr* 1983;276(2):456–462.

44 Oddie CJ, Jackman GP, Bobik A. Analysis of milrinone in plasma using solid-phase extraction and high-performance liquid chromatography. *J Chromatogr* 1986;374(1):209–214.

45 Woolfrey SG, Hegbrant J, Thysell H, *et al.* Dose regimen adjustment for milrinone in congestive heart failure patients with moderate and severe renal failure. *J Pharm Pharmacol* 1995;47(8):651–655.

46 Lynn AM, Sorensen GK, Williams GD, *et al.* Hemodynamic effects of amrinone and colloid administration in children following cardiac surgery. *J Cardiothorac Vasc Anesth* 1993;7(5):560–565.

47 U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Veterinary Medicine (CVM). Guidance for industry - Bioanalytical method validation 2001. http://www.fda.gov/downloads/Drugs/Guidances/ucm070107.pdf. Accessed 17 Mar 2013.

48 Jönsson S, Henningsson A. Regulatory vision of paediatric applications. http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500009845.pdf. Accessed 16 Mar 2013.

49 Zhao P, Rowland M, Huang S. Best practice in the use of physiologically based pharmacokinetic modeling and simulation to address clinical pharmacology regulatory questions. *Clin Pharmacol Ther* 2012;92(1):17–20.

50 Leong R, de Vieira MLT, Zhao P, *et al.* Regulatory experience with physiologically based pharmacokinetic modeling for pediatric drug trials. *Clin Pharmacol Ther* 2012;91(5):926–931.

51 Zhao P, de Vieira MLT, Grillo JA, *et al.* Evaluation of exposure change of nonrenally eliminated drugs in patients with chronic kidney disease using physiologically based pharmacokinetic modeling and simulation. *J Clin Pharmacol* 2012;52(1 Suppl):91S-108S.

52 U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for industry: Drug interaction studies - Study design, data analysis, implications for dosing, and labeling recommendations: Draft guidance 2012.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf. Accessed 17 Mar 2013.

53 International Programme on Chemical Safety (IPCS). Characterization and application of physiologically based pharmacokinetic models in rik assessment: Harmonization project document no. 9, 1st Edn. Geneva, Switzerland: WHO Library Cataloguing-in-Publication Data 2010.

54 Ralph LD, Sandstrom M, Twelves C, *et al.* Assessment of the validity of a population pharmacokinetic model for epirubicin. *Br J Clin Pharmacol* 2006;62(1):47–55.

55 Pasquali SK, Hall M, Slonim AD, *et al.* Off-label use of cardiovascular medications in children hospitalized with congenital and acquired heart disease. *Circ Cardiovasc Qual Outcomes* 2008;1(2):74–83.

56 Kastrup M, Markewitz A, Spies C, *et al.* Current practice of hemodynamic monitoring and vasopressor and inotropic therapy in post-operative cardiac surgery patients in Germany: results from a postal survey. *Acta Anaesthesiol Scand* 2007;51(3):347–358.

57 Oldner A, Rossi P, Karason S, *et al.* A practice survey on vasopressor and inotropic drug therapy in Scandinavian intensive care units. *Acta Anaesthesiol Scand* 2003;47(6):693–701.

58 Leone M, Vallet B, Teboul J, *et al.* Survey of the use of catecholamines by French physicians. *Intensive Care Med* 2004;30(5):984–988.

59 Barrett JS, Narayan M, Patel D, *et al.* Prescribing habits and caregiver satisfaction with resources for dosing children: Rationale for more informative dosing guidance. *BMC Pediatr* 2011;11:25.

60 Committee on Quality of Health Care in America, Institute of Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century, 1st Edn. Washington, DC: National Academies Press 2001.

61 Ring JC. Pharmacotherapy for pediatric cardiovascular diseases: the role of off-label drug use in the 21st century. *Circ Cardiovasc Qual Outcomes* 2008;1(2):69–71.

62 National Institutes of Health. List of drugs for which pediatric studies are needed. *Federal Register* 2003;68(13):2789–2790.

63 McLay JS, Tanaka M, Ekins-Daukes S, *et al.* A prospective questionnaire assessment of attitudes and experiences of off label prescribing among hospital based paediatricians. *Arch Dis Child* 2006;91(7):584–587.

64 Mukattash T, Hawwa AF, Trew K, *et al.* Healthcare professional experiences and attitudes on unlicensed/off-label paediatric prescribing and paediatric clinical trials. *Eur J Clin Pharmacol* 2011;67(5):449–461.

65 Mukattash TL, Wazaify M, Khuri-Boulos N, *et al.* Perceptions and attitudes of Jordanian paediatricians towards off-label paediatric prescribing. *Int J Clin Pharm* 2011;33(6):964–973.

66 Lenk C, Koch P, Zappel H, *et al.* Off-label, off-limits? Parental awareness and attitudes towards off-label use in paediatrics. *Eur J Pediatr* 2009;168(12):1473–1478.

67 Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005;6(1):2–8.

68 Neubert A, Wong ICK, Bonifazi A*, et al.* Defining off-label and unlicensed use of medicines for children: results of a Delphi survey. *Pharmacol Res* 2008;58(5-6):316–322 .

69 Li JS, Cohen-Wolkowiez M, Pasquali SK. Pediatric cardiovascular drug trials, lessons learned. *J Cardiovasc Pharmacol* 2011;58(1):4–8.

70 Baiardi P, Giaquinto, C, Girotto, S*, et al.* Innovative study design for paediatric clinical trials. *Eur J Clin Pharmacol* 2011;67 Suppl 1:109–115.

71 Jadhav PR, Kern SE. The need for modeling and simulation to design clinical investigations in children. *J Clin Pharmacol* 2010;50(9 Suppl):121S-129S.

72 Manolis E, Osman TE, Herold R*, et al.* Role of modeling and simulation in pediatric investigation plans. *Paediatr Anaesth* 2011;21(3):214–221.

73 Brierley J, Carcillo JA, Choong K*, et al.* Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med* 2009;37(2):666–688.

74 Hayton WL. Maturation and growth of renal function: dosing renally cleared drugs in children. *AAPS PharmSci* 2000;2(1):22–28.

75 Palomba H, de Castro I, Neto ALC*, et al.* Acute kidney injury prediction following elective cardiac surgery: AKICS Score. *Kidney Int* 2007;72(5):624–631.

76 Bishara T, Seto WT, Trope A*, et al.* Use of Milrinone in Critically Ill Children. *CJHP* 2010;63(6):420–428.

77 Vazir A, Leaver N, Lyster H*, et al.* Is monitoring milrinone therapy useful in advanced heart failure? *Int J Cardiol* 2011;149(3):380–381.

78 Antila S, Sundberg S, Lehtonen LA. Clinical pharmacology of levosimendan. *Clin Pharmacokinet* 2007;46(7):535–552.

79 McNamara PJ, Shivananda SP, Sahni M*, et al.* Pharmacology of milrinone in neonates with persistent pulmonary hypertension of the newborn and suboptimal response to inhaled nitric oxide. *Pediatr Crit Care Med* 2013;14(1):74–84.

80 Price JF, Towbin JA, Dreyer WJ*, et al.* Outpatient continuous parenteral inotropic therapy as bridge to transplantation in children with advanced heart failure. *J Card Fail* 2006;12(2):139–143.

81 Anderson BJ, Merry AF. Data sharing for pharmacokinetic studies. *Paediatr Anaesth* 2009;19(10):1005–1010.

Results from the PubMed search (http://www.ncbi.nlm.nih.gov/pubmed) from March 17th, 2013

for

(((("Infant"[Mesh]) OR "Infant, Newborn"[Mesh]) AND "Cardiac Output, Low"[Majr]) AND "Review" [Publication Type]

1: Meyer S, Gortner L, Brown K, Abdul-Khaliq H. The role of milrinone in children with cardiovascular compromise: review of the literature. Wien Med Wochenschr. 2011 Apr;161(7-8):184-91. doi: 10.1007/s10354-011-0869-7. Epub 2011 Mar 7.

Review. PubMed PMID: 21360291.

2: Ascenzi JA, Kane PL. Update on complications of pediatric cardiac surgery. Crit Care Nurs Clin North Am. 2007 Dec;19(4):361-9, v.

Review. PubMed PMID: 18022522.

3: Momma K. ACE inhibitors in pediatric patients with heart failure. Paediatr Drugs. 2006;8(1):55-69.

Review. PubMed PMID: 16494512.

4: Kluckow M. Low systemic blood flow and pathophysiology of the preterm transitional circulation. Early Hum Dev. 2005 May;81(5):429-37.

Review. PubMed PMID: 15935920.

5: Osborn DA. Diagnosis and treatment of preterm transitional circulatory compromise. Early Hum Dev. 2005 May;81(5):413-22. Epub 2005 Apr 21.

Review. PubMed PMID: 15935918.

6: Cohen G, Permut L. Decision making for mechanical cardiac assist in pediatric cardiac surgery. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2005:41-50.

Review. PubMed PMID: 15818357.

7: Cuadrado AR. Management of postoperative low cardiac output syndrome. Crit Care Nurs Q. 2002 Nov;25(3):63-71.

Review. PubMed PMID: 12450160.

8: Wessel DL. Managing low cardiac output syndrome after congenital heart surgery. Crit Care Med. 2001 Oct;29(10 Suppl):S220-30.

Review. PubMed PMID: 11593065.

9: Kluckow M, Evans N. Low systemic blood flow in the preterm infant. Semin Neonatol. 2001 Feb;6(1):75-84.

Review. PubMed PMID: 11162287.

10: Tuo P, Calza G, Moretti R, Pallecchi AE, Pessagno A, Balzarini C, Tumolo M, Fossa S. [Role of extracorporeal circulation in reversible acute cardiorespiratory insufficiency in neonatal and pediatric intensive care]. Pediatr Med Chir. 1995 Jan-Feb;17(1):33-6.

Review. Italian. PubMed PMID: 7739924.

11: Zwischenberger JB, Cox CS Jr. ECMO in the management of cardiac failure. ASAIO J. 1992 Oct-Dec;38(4):751-3.

Review. PubMed PMID: 1450468.

12: Bartlett RH. Extracorporeal life support for cardiopulmonary failure. Curr Probl Surg. 1990 Oct;27(10):621-705.

Review. PubMed PMID: 2209070.

13: Keeley SR, Bohn DJ. The use of inotropic and afterload-reducing agents in neonates. Clin Perinatol. 1988 Sep;15(3):467-89.

Review. PubMed PMID: 3066549.

<30th October 2012>

Submission of comments on 'Inventory of paediatric medicines – Cardiovascular therapeutic area' (EMA/550070/2012)

Comments from:

Name of organisation or individual
Winnie Vogt (BPharm, MSc Clin Pharm), Germany

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Drugs for the PREVENTION of low cardiac output syndrome (LCOS) in neonates, infants and children with open heart surgery are increasingly used across Europe (Paediatr Anaesth 2011;21(12):1176-84, Intensive Care Med 2011;37(8):1390-1). The use is completely off-label with insufficient evidence supporting the variety of 1) drugs, 2) drug combinations and 3) dosing regimens administered to 4) various paediatric patients in clinical practice. These aspects should be discussed and addressed by the 'Inventory of paediatric medicines' and a clear distinction made between paediatric needs for LCOS prevention and treatment. The drugs most commonly used for LCOS prevention are milrinone, dopamine, dobutamine, epinephrine, levosimendan, methylprednisolone, enoximone and glyceryl trinitrate (see above references). There is also a need for an international consensus on the definition of "low cardiac output syndrome" to know what to treat and/or prevent and enable comparability of study results. Off-label drugs commonly used for the TREATMENT of paediatric LCOS across Europe (Arch Dis Child	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	2011;96(12):1180-6) and not listed in the "Inventory for paediatric medicines" are: - Epinephrine (licensed for cardiopulmonary resuscitation), - Glyceryl trinitrate (not licensed for use in children), - Enoximone (licensed only for use in children less than 12 years and lack of pharmacokinetic data), - Prostacyclin derivatives (licensed only for temporarily maintaining the patency of the ductus arteriosus in infants with congenital heart disease). Consequently, the paediatric needs resulting from this particular off-label drug use should also be discussed and addressed.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Levosimendan		Comment: under "Needs" to include the indication low cardiac output syndrome especially after cardiac surgery (treatment and prevention) Proposed change (if any):	
Dopamine		Comment: under "Needs" to include the indication low cardiac output syndrome especially after cardiac surgery (treatment and prevention). The PIP is agreed upon treatment of hypotension in the extremely low gestational age newborn and treatment of hypotension in children. Proposed change (if any):	
Nitroprusside		Comment: under "Needs" to include the indication low cardiac output syndrome especially after cardiac surgery (treatment and prevention) Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 April 2013
EMA/PDCO/246339/2013
Human Medicines Development and Evaluation

Inventory of paediatric therapeutic needs

Cardiovascular therapeutic area

Agreed by PDCO	August 2012
Adopted by PDCO for release for consultation	15-17 August 2012
Start of public consultation	30 August 2012
End of consultation (deadline for comments)	30 October 2012
Agreed by PDCO	November 2012
Adoption by PDCO for final release	7 December 2012

Objective of the list

Based on Article 43 of the European Union Paediatric Regulation the Paediatric Committee at the European Medicines Agency (PDCO) is working to establish an inventory to identify the needs in the different therapeutic areas where there should be research and development of medicinal products for children. The inventory is based on the results of a survey of all paediatric uses of medicines in Europe and on the existing list of paediatric needs established by the former Paediatric Working Party; it will be published progressively by therapeutic area. Further information can be found on the EMA website.

Disclaimer

The lists should not be viewed as a prescription tool nor as recommendations for treatment.

The authorisation status of the medicinal products as well as on available formulation(s) was taken into account, however, this information is limited and not available for all European Member States. Users of this list are therefore advised to check the authorisation status of the medicinal products of interest.

The methodology used to establish the list was based as much as possible on existing evidence. It is, however, acknowledged that identification of needs for research into medicinal products for paediatric use is partly based on subjective criteria and may change over time and according to region. This may

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also be the case should further information of which the PDCO is not aware become available (e.g. on pharmacokinetics, safety and efficacy, submission of Paediatric Investigation Plans on listed products, etc.).

Notes

For the designation of the products International Non-proprietary Names (INN) are used whenever possible. Products are listed in alphabetical order within the product classes, not in any order of priority.

If not stated otherwise, the needs concern all paediatric age-groups.

The shaded products represent those where a positive decision has been adopted on a Paediatric Investigation Plan (PIP). For further information please consult the EMA website.

CARDIOVASCULAR THERAPEUTIC AREA

Refer to the therapeutic areas of **nephrology** [e.g. for ACE-inhibitors, diuretics, calcium-antagonists, AT-II receptor antagonists ('sartans')] and **metabolism** [e.g. for 'statins'] as soon as they are published.

Product	**Needs**
Inotropes, Phosphodiesterase Inhibitors, Inodilators, Vasodilators	
Arginine-vasopressin	For treatment of cardiogenic shock: • Data on PK/dose, safety and efficacy • Age appropriate formulation
Bosentan	PIP agreed for 'treatment of pulmonary arterial hypertension (PAH)'
Dobutamine	PIP agreed for 'treatment of neonatal circulatory failure'
Dopamine	PIP agreed for 'treatment of vascular hypotension disorder'
	For prevention and treatment of low cardiac output syndrome (LOCS): • Data on safety and efficacy
Epinephrine (adrenaline)	For prevention and treatment of low cardiac output syndrome (LOCS): • Data on dose, safety and efficacy • Age appropriate formulation for neonates.
Levosimendan	For treatment of heart failure, and prevention and treatment of low cardiac output syndrome (LOCS): • Data on dose, safety and efficacy
Nitric oxide (NO)	For treatment of persistent pulmonary hypertension of the newborn (PPHN): • Data on efficacy and safety in preterm infants below 34 weeks of gestational age (GA)
Nitroprusside	For treatment of heart failure and hypertensive crisis, and prevention and treatment of low cardiac output syndrome (LOCS): • Data on PK/dose, safety and efficacy • Age appropriate formulation
Norepinephrine	For treatment of acute hypotension: • Data on PK/dose, safety and efficacy in children including preterm and term neonates • Age appropriate formulation
Prostracyclin and related analogues	For pulmonary hypertension and treatment of low cardiac output syndrome (LOCS): • Data on PK, safety and efficacy

Product	Needs
Sildenafil	PIP agreed for 'treatment of pulmonary arterial hypertension'
Anti-hypertensive (central action mechanism)	
Clonidine	For treatment of hypertension: • Data on PK/dose, safety and efficacy • Age appropriate oral formulation
α- and β-Blockers	
Labetalol	For treatment of hypertension: • Data on PK/dose, safety and efficacy • Age appropriate formulation
β-Blockers	
Atenolol	For treatment of hypertension and arrhythmias: • Data on PK/dose, safety and efficacy in children below 12 years of age including neonates
Bisoprolol	For treatment of chronic heart failure: • Data on PK/dose, safety and efficacy • Age appropriate formulation
Carvedilol	For treatment of hypertension and heart failure: • Data on PK/dose, safety and efficacy • Age appropriate formulation
Esmolol	For treatment of hypertension and arrhythmias: • Data on PK/dose, safety and efficacy • Age appropriate formulation
Metoprolol	For treatment of hypertension and arrhythmias: • Data on PK/dose, safety and efficacy • Age appropriate formulation
Propranolol	For treatment of hypertension and supraventricular tachycardia: • Data on PK/dose, safety and efficacy
Sotalol	For treatment of supraventricular and ventricular arrhythmias: • Data on PK/dose, safety and efficacy • Age appropriate formulation

Product	Needs
Other Anti-arrhythmics	
Adenosine phosphate	For cardioversion and treatment of supraventricular tachycardia: • Data on dose, safety and efficacy • Age appropriate formulation
Amiodarone	For treatment of arrhythmias: • Data on PK/dose, safety and efficacy • Age appropriate formulation
Flecainide	For treatment of arrhythmias: • Data on PK/dose, safety and efficacy in children below the age of 12 years • Age appropriate formulation
Anti-thrombotics	
Acetylsalicylic acid (aspirin)	For treatment of Kawasaki disease: • Age appropriate formulation For prevention of thromboembolic events: • Data on safety and efficacy • Age appropriate formulation
Alteplase	For intravascular and catheter related thrombolysis: • Data on PK/dose, safety and efficacy • Age appropriate formulation
Clopidogrel	PIP agreed for 'prevention of thromboembolic events'
Low molecular weight heparins	For prevention and treatment of thrombosis: • Data on PK/dose, safety and efficacy • Age appropriate formulation
Urokinase	For intravascular thrombolysis: • Data on PK/dose, safety and efficacy
Warfarin	For prevention and treatment of venous thrombosis and pulmonary embolism: • Data on PK/dose, safety and efficacy • Age appropriate formulation

Abbreviations:

PIP	Paediatric Investigation Plan
PK	pharmacokinetics

Appendix

FROM SUMMARY TO ABOUT THE AUTHOR

Open heart surgery can be a life-saving endeavour for neonates, infants and children born with congenital heart defects. Thus, it is even more important to ensure successful clinical patient outcome by preventing or timely treating low cardiac output syndrome (LCOS), which is the main determinate of perioperative morbidity and mortality in paediatrics. Albeit the clinical seriousness of LCOS, drug therapy is characterised by the lack of prescribing guidance and incomplete pharmacokinetic understanding of the drug-disease interaction that governs drug exposure. Consequently, this thesis aims at improving our understanding of drug therapy for LCOS towards safeguarding prescribing for paediatric patients.

To accomplish this aim, current hospital prescribing practice was determined and analysed by conducting a web-based survey on the pharmacological management of LCOS in paediatric patients with open heart surgery, short EuLoCOS-Paed, across European hospitals specialised in paediatric open heart surgery, in which 90 of 125 eligible hospitals from 31 European countries participated between January and August 2009. As the results of EuLoCOS-Paed, treatment algorithms were presented for LCOS with elevated and low systemic vascular resistance as well as elevated pulmonary vascular resistance. A highly variable drug use for paediatric LCOS treatment and prevention was disclosed with regard to individual drug use, drug combinations, therapeutic drug classes and most importantly, paediatric research needs were identified. Overall, milrinone was shown to be the drug of choice for paediatric LCOS across Europe and to have the highest variability in the mode of drug administration. Therefore, milrinone was embraced in a novel physiology-based pharmacokinetic (PBPK) drug-disease model to evaluate current dosing strategies and study the impact of disease, open heart surgery and age on drug exposure. Model development and external evaluation was successfully undertaken and highlighted a non-linear dependence of milrinone plasma clearance on paediatric age, an increased non-renal clearance with impaired kidney function and significant drug exposure differences between paediatric patients with and without LCOS and between adults and paediatrics. In all, current milrinone prescribing for LCOS was predicted unable to maintain the recommended therapeutic plasma levels of milrinone and, therefore, optimised dosing regimens were developed that considered the exposure differences due to age and disease.

The results of this thesis highlight the lack of evidence-based therapy for paediatric LCOS, which is an ongoing dilemma that warrants special attention by all stakeholders directly and indirectly involved in the care of paediatric patients with open heart surgery. It is only by their awareness and combined effort in tackling the hurdles that these patients can benefit from safer and more effective drug therapy in future. Thus, the results of the thesis are hoped to positively impact future milrinone prescribing and research endeavours in this field at the same time as strengthening the role of paediatric PBPK drug-disease modelling and simulation.

Operationen am offenen Herzen können für Neugeborene, Säuglinge und Kinder mit angeborenen Herzfehlern lebensrettend sein. Die Verhinderung bzw. zeitnahe Behandlung des Low Cardiac Output Syndroms (LCOS) ist daher zwingend für einen erfolgreichen Operationsausgang, da es die Hauptursache für die perioperative Morbidität und Mortalität darstellt. Trotz des akuten lebendsbedrohlichen Krankheitsbildes von LCOS ist die medikamentöse Therapie jedoch durch einen Mangel an zugelassenen Arzneimitteln und Verständnis der pharmakokinetischen und -dynamischen Wechselwirkungen zwischen Arzneistoff und Krankheitsbild im menschlichen Körper gekennzeichnet. Ziel dieser Arbeit ist es daher, einen Beitrag zum verbesserten Verständnis und zur Sicherstellung der medikamentösen Therapie für Kinder mit LCOS zu leisten.

Um dieses Ziel zu erreichen, wurde im ersten Schritt das Verschreibungsverhalten in 90 von 125 möglichen Krankenhäusern aus 31 europäischen Ländern mit Hilfe einer internetgestützten Umfrage zum medikamentösen Einsatz bei pädiatrischen Patienten mit LCOS nach Operation am offenen Herzen, kurz EuLoCOS-Paed, erfasst und ausgewertet. Als Ergebnis liegen zum ersten Mal Behandlungsalgorithmen für LCOS mit erhöhtem bzw. niedrigem systemischen Gefäßwiderstand und erhöhtem pulmonalen Gefäßwiderstand vor; zusätzlich wurde die Wichtigkeit der präventiven Gabe von Arzneistoffen im klinischen Alltag deutlich. Insgesamt konnte aber auch gezeigt werden, dass die medikamentöse Therapie extrem variabel ist, woraus dringend erforderlicher pädiatrischer Forschungsbedarf, insbesondere für Milrinon, abgeleitet werden konnte. Aus diesem Grund wurde Milrinon im nächsten Schritt der Doktorarbeit in ein neuartiges physiologiebasiertes pharmakokinetisches (PBPK) Arzneimittel-Krankheitsmodell eingeschlossen, welches den Einfluss von Krankheit, Operation und Patientenalter auf die Milrinonexposition berücksichtigte. Mit Hilfe dieses Modelles konnten eine nicht-lineare Altersabhängigkeit der Elimination von Milrinon bei pädiatrischen Patienten und grundlegende Unterschiede in der Arzneistoffexposition zwischen erwachsenen und pädiatrischen Patienten als auch jenen mit und ohne LCOS festgestellt werden. Zusätzlich wurde deutlich, dass die derzeitigen Dosierungen nur unzureichend die empfohlenen therapeutischen Plasmaspiegel von Milrinon erreichen. Daher wurden optimierte Dosierungsschemata entwickelt, die dem Alter und Krankheitszustand entsprechend Rechnung tragen, um so eine sichere und wirksame LCOS-Therapie zu ermöglichen.

Zusammenfassend unterstreichen die Ergebnisse dieser Arbeit den Mangel an evidenzbasierter Medizin für pädiatrisches LCOS, welche aufgrund der Schwere des Krankheitsbildes eine besondere Vigilanz und gemeinsame Anstrengungen sämtlicher an der Pflege der Patienten beteiligten Berufsgruppen zwingend notwendig machen. Die optimierten Dosierungsschemata für Milrinon mit Hilfe von Modellbildung und Simulation zielen zudem auf einen verbesserten Arzneimitteleinsatz als auch auf die verstärkte Nutzung von PBPK arzneimittelgekoppelten Krankheitsmodellen zur Therapieoptimierung in der Pädiatrie ab.

I would like to thank Prof. Dr. S. Läer for giving me the opportunity to conduct the PhD research at the Department of Clinical Pharmacy and Pharmacotherapy at Heinrich-Heine-Universität Düsseldorf.

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PUBLICATIONS WITH PEER-REVIEW

- Vogt W. Evaluation and optimisation of current milrinone prescribing for the treatment and prevention of low cardiac output syndrome in paediatric patients after open heart surgery using a physiology-based pharmacokinetic drug-disease model. *Clin Pharmacokinet* 2014;53(1):51-72.
- Vogt W, Läer S. Treatment for paediatric low cardiac output syndrome: Results from the European survey EuLoCOS-Paed. *Arch Dis Child* 2011;96(12):1180-6.
- Vogt W, Läer S. Prevention for pediatric low cardiac output syndrome: results from the European survey EuLoCOS-Paed. *Paediatr Anaesth* 2011;21(12):1176-84.
    i. Accompanied by an editorial from A. van Saet and S. N. de Wildt, Erasmus MC, Rotterdam, Netherlands.
    ii. Being selected the favourite paper from recent literature at the 2013 Annual Meeting of the Congenital Cardiac Anesthesia Society.
    iii. Being selected the favourite paper from recent literature at the 2013 Winter Meeting of the Society for Pediatric Anesthesia.
- Vogt W, Läer S. Drug use patterns for the prevention of paediatric low cardiac output syndrome in Europe. *Intensive Care Med* 2011;37(8):1390-1.

PUBLICATIONS WITHOUT PEER-REVIEW

- Vogt W, Frobel A-K, Läer S. Besonderheiten der Pharmakotherapie bei Kindern. Gibt es eine Metamorphose der ``therapeutischen Waisen"?. *Pharm Unserer Zeit* 2009;38(1):22-9.
- Vogt W, Läer S. Vermeidet Metformin eine Gewichtszunahme unter atypischen Antipsychotika?. *AVP* 2008;35(6):117-8.
- Vogt W, Läer S. Gewichtszunahme als unerwünschte Wirkung vieler Arzneimittel. *AVP* 2008;35(4):78-79.

CONFERENCE PRESENTATIONS

- Vogt W. Paediatric PBPK drug-disease modelling and simulation towards optimisation of drug therapy: an example of milrinone for the treatment and prevention of low cardiac output syndrome in paediatric patients after open heart surgery. In Abstracts of the 22nd Annual Meeting of the Population Approach Group in Europe - PAGE, Glasgow, Scotland (2013).
- Vogt W, Läer S. European survey on the pharmacological management of low cardiac output syndrome in children undergoing cardiac surgery with cardiopulmonary bypass (EuLoCOS-Paed). In Proceedings of the 12th ESDPPP Congress, Chamonix, France (2009).
- Jaffan L, Vogt W, Läer S. Drug-related problems on paediatric wards: Proposing a "PCNE for children" for hospital quality management in paediatric pharmacotherapy. In Proceedings of the 12th ESDPPP Congress, Chamonix, France (2009).
- Hsien L, Vogt W, Läer S. Simulation of sildenafil disposition in virtual children by means of physiologically based pharmacokinetic modelling. *Naunyn Schiedebergs Arch Pharmacol* 2009;379(Suppl 1):4798.
- Vogt W, Frobel A-K, Ramusovic S, *et al*. The in silico child helps to design paediatric dosing regimens a priori: an example with Milrinone. *Clin Res Cardiol* 2008;97:707.
- Vogt W, Ramusovic S, Frobel A-K, *et al*. Evaluation of a physiologically based pharmacokinetic model of milrinone for children undergoing cardiac surgery. In Proceedings of the 11th ESDP Congress Safe and effective medicines for children, Rotterdam, Netherlands, pp.94 (2008).
- Vogt W, Stewart L, Hudson S. A tool for assessing patients' self-administration of medicines: an evaluation in patients with rheumatoid arthritis. *Pharm World Sci* 2009;31:2634.

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