The Efficacy of Transitioning Patients With Pulmonary Hypertension From Phosphodiesterase Type 5 Inhibitors To Riociguat: A Systematic Analysis And Retrospective Chart-Review

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Research Article

Keywords: PDE5i, riociguat, pulmonary arterial hypertension, 6MWTD

Posted Date: July 29th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-736551/v1

Abstract

Purpose: Pulmonary arterial hypertension (PAH) is a rare, progressive disease with significant mortality. Phosphodiesterase type 5 inhibitors (PDE5i) are an effective therapy, however, patients often progress despite treatment. This review examined the efficacy of transitioning patients from a PDE5i to riociguat by analyzing changes in the 6-minute walk test distance (6MWTD) and hemodynamic parameters in adults with PAH.

Methods: This was a combined systematic review and meta-analysis of current literature (Jan 2013 – Oct 2019) and a retrospective database study (Jan 2013-Aug 2017) from a tertiary pulmonary hypertension center in Ontario, Canada. All English language studies were searched through PubMed, EMBASE, the Web of Science and EBSCO from 2013 to 2019. Results were combined using a random effect model. We used an I^2 statistic estimate (percent) to quantify inconsistency.

Results: The results were combined from a total of 6 published studies (4 cohort studies, 1 case report and 1 case series), and a retrospective database study. Mean difference across studies demonstrates a 6MWTD improvement of 43.7m (CI 3.72- 83.7, P=0.03, I^2=77%), favouring riociguat. There was an improvement in all the secondary outcomes examined, including World Health Organization functional class, mean pulmonary arterial pressure, pulmonary vascular resistance and cardiac index, demonstrating a propensity to favour riociguat.

Conclusion: This review demonstrates significant improvement in both clinical and hemodynamic outcomes when patients with PAH are transitioned to riociguat from PDE5i. However, the number of studies included was small, and the quality of studies was moderate with limited evidence regarding outcomes of interest.

PROSPERO registration #: CRD42020154661

Registered April, 2020

Introduction

Pulmonary arterial hypertension (PAH) is a rare and progressive disorder associated with significant morbidity and mortality[1]. PAH is characterized by vascular dysfunction involving an imbalance in the activity of the endothelin-1, prostacyclin and the nitric oxide (NO) pathways [1, 2]. Over the long-term, this results in progressive increases in pulmonary vascular resistance (PVR) and ultimately right heart failure, decompensation and death [3–4].

Riociguat is a promising therapy which acts on the NO pathway, both by augmenting the interaction between NO and soluble guanylate cycloase (sGC), and by stimulating sGC independent of NO, leading to increased pulmonary vasculature dilatation [5–7]. Recent literature shows encouraging benefits not only with regards to objective hemodynamic parameters such as pulmonary vascular resistance, but also in terms of important clinical outcomes such as an increased 6-minute walk test distance (6MWTD), improvement in the World Health Organization functional class (WHO FC) score and patient symptom scores [5–8].

However, the rare nature of this disease with an estimated prevalence of 4.6 to 26 per million adults represents a significant challenge for the clinical assessment of new therapies [9]. Therefore, given the limited number of accessible medications to individuals with idiopathic PAH and the promising effects of riociguat, there is a need for a systematic review to analyze data about the safety and efficacy of transition of therapy to riociguat in patients who fail PDE5i therapy. The primary aim of this study was to examine the benefit of transitioning patients from a PDE5i to riociguat.

Methods

This protocol was registered with PROSPERO: CRD42020154661. We combined a meta-analysis of current literature and a retrospective database study from the University of Ottawa Heart Institute (UOHI) Pulmonary Hypertension clinic located in Ottawa, Ontario, Canada. The retrospective database study was approved by the Research Ethics Board at the Ottawa Hospital Research Institute.

Databases searched included PubMed, EMBASE, the Web of Science and EBSCO from Jan 2013 - Oct 2019. All English language studies were screened. See Appendix: eAppendix 1 for search terms. For the systematic review, all adult patients (≥ 18 years) diagnosed with PAH on a PDE5i, who were subsequently transitioned to riociguat were included. Any patients with prior treatment on riociguat was excluded. For the retrospective database study, all group 1 PAH patients, over the age of 18 who failed therapy with PDE5i (which is defined as any of: cardiac index (CI) ≤ 2.5, WHO FC ≥ III or 6MWTD less than predicted) and subsequently transitioned to riociguat were included. To be included, patients must have had a right heart catherization (RHC) with PVR of ≥ 300dyn-sec-cm^{-5} or mean pulmonary arterial pressure (mPAP) of ≥ 25mmHg or pulmonary wedge pressure (PCWP) of ≤ 15mmHg. The patient's clinic charts were reviewed from the periods between January 30 2013 to August 31, 2017 and analyzed.

We included randomized controlled trials and longitudinal observational studies (prospective or retrospective cohort studies and case control studies). We excluded any non-English articles, review articles, case reports, letters to the editor, conference abstracts and any irretrievable studies. For the systematic review: two authors (K.S. and T. K.) independently screened in a stepwise manner, the titles, then abstracts, and finally the full article of studies retrieved using the pre-specified search strategy (Appendix S1) to identify studies that met the inclusion criteria. Disagreements were resolved through discussion and if required, a senior author (G.C.) was consulted. A standardized form was used to extract data from the included studies. The data extracted included specific details about the study, study setting (e.g., clinical vs. community-based study), populations (participant demographics and baseline characteristics), details of the definition(s) of pulmonary hypertension, specific PDE5i and dosage prior to transition, the reason for transition, results post transition and any mortality or morbidity data.

For the retrospective database study, clinical data was collected on each eligible patient from a detailed chart review. These included: age, gender, medical record number, hemodynamic measurements obtained from RHC, echocardiogram, current and previous relevant co-morbidities (ie pulmonary embolism, rheumatological diseases, surgical pulmonary endarterectomies etc.). Furthermore, medication history, especially use of any calcium channel blocker use, diuretics, anticoagulation, endothelin receptor agonists, PDE5 inhibitor, prostaglandin analogues, and soluble guanylate cyclase was recorded.

The primary outcome was the change in the 6MWTD post-transition from PDE5i to riociguat. The secondary outcomes were the post transition changes in: (1) WHO FC; (2) Hemodynamic data: CI, mPAP, PCWP and B-type natriuretic peptide levels (BNP); (3) time to clinical worsening defined by hospitalizations and lung transplantation, any observed adverse side effects and mortality.

Study results were synthesized through tabulation and qualitative description. Data regarding the stated outcomes of the review (standardized mean difference (SMD) or mean difference (MD) for continuous) were extracted. Pooled results were presented as forest plots. We anticipated a limited scope for meta-analysis due to high methodological, clinical and statistical heterogeneity between studies. Thus, results were combined using a random effect model. Heterogeneity was assessed using the Cochran's Q-test of (residual) heterogeneity; a p-value of less than 0.10 was considered to represent evidence of heterogeneity. To quantify inconsistency, we used an I^2 statistic estimate (percent), which assesses how much of the total variability in the effect size estimates can be attributed to heterogeneity between studies. We considered an I^2 value greater than 50% to be indicative of substantial heterogeneity. The R software was used for data analysis. For the retrospective database study, descriptive statistics were used to characterize the sample of interest. The Wilcoxon signed-rank test was used to compare continuous outcomes; the McNemar's Chi-squared test with continuity correction was used for categorical outcomes. Generalized linear mixed regression models were used to adjust for confounders. Given the small sample size, only age was considered in the statistical model as a potential confounder.

We planned for one reviewer (K.S.) to assess for the risk of bias for each study using either the Cochrane Handbook for Systematic Reviews for randomized controlled trials or the Newcastle-Ottawa scale (NOS) for observational trials [10, 11]. Results were corroborated by a second reviewer (T. K.). There were no randomized control trials and thus only the Newcastle-Ottawa scale was used.

The NOS uses a 'star system' to evaluate studies on three domains: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively [11]. The scale evaluates the domains of selection, comparability and outcome or exposure [11]. Although there is no formalized

process of grading the quality of studies per the NOS, previous studies have employed a score of 7 or higher to be considered high quality studies [12].

Results

The primary search process identified 366 articles with 79 duplicates (Fig. 1). Of the 286 articles screened, 263 were determined to be irrelevant based on prior identified inclusion criteria and were excluded based on the title and abstract screening. 22 articles proceeded to full screening and out of those, 16 were excluded because 11 were only abstracts, 2 were overviews of published studies and 1 was inaccessible. Although the *a priori* identified exclusion criteria excluded case series and case reports, due to the paucity of available literature, 1 case series and 1 case report were ultimately included in the final analysis, yielding a total of 6 included articles. In addition, we included an unpublished database study from a Pulmonary Hypertension Clinic at tertiary center located in Ottawa, Canada at the UOHI for a total of 7 studies.

There was a wide range of study designs, including 1 case reports, 1 case series, 3 retrospective cohort studies and 1 prospective cohort along with the primary retrospective database study. The studies were conducted predominantly in North America and Europe with 1 study from Japan (Table 1) [8, 13–17]. On average, subjects were in their late 50s with mean age ranging from 47 to 59. These participants were predominantly female (Table 1) with a pre-transition WHO FC of II-III (Table S2). All the participants had a diagnosis of group one PAH with the exception of the Kuroda et al. study in which 1 of the 7 participants had a diagnosis of chronic thromboembolic pulmonary hypertension [15]. Primary outcomes were quite heterogeneous, with studies examining either clinical outcomes, such as a change in 6MWTD and WHO FC, or hemodynamic endpoints such as change in mPAP (Table 1) [8, 13–17]. The transition protocol is displayed in Table 2. Three of 7 studies had a 24h washout period for sildenafil, one study had a washout period of 12h and another had no washout period [8, 13–17]. Tadalafil washouts also were variable from 24 to 72h documented [8, 16]. Titration protocols were similar with most studies starting at a dose of 1mg of riociguat TID and titrating up by 0.5mg to a targeted dose of 2.5mg TID [8, 13–17].

There were no randomized control trials found through literature search and studies found were predominantly retrospective cohort studies (4/7 studies), and most had limitations in terms of study quality. Thus, only the Newcastle-Ottawa scale was used to assess for risk of bias. This analysis was not possible for the Poch and Raina et al. studies since they are a case report or case series, respectively [13, 17]. Due to the low prevalence of PAH, there was no control group, and in each cohort, PAH patients were compared to their own pre-transition values. Furthermore, small sample size in these studies contributed to an increased risk of bias. The significant dropout rate of 17% in the RESPITE study suggests the risk of attrition bias. Overall, the studies did not meet criteria for high quality studies and all had a NOS of 6 or lower (Table S3).

The primary outcome of the study was the mean change in 6MWTD. There were only 4 studies which could be pooled with a random-effects model as Kuroda et al. did not report 6MWTD data, Poch was a case study and Raina et al. only reported 6MWTD for one of the 3 case series patients [13, 16, 17]. As seen in Fig. 2, there was high heterogeneity among the results with an I^2 value of 77%. Overall, the mean difference across studies demonstrates a 6MWTD improvement of 43.7m (CI 3.72–83.7, p = 0.03), favouring riociguat and meeting a minimal clinically important difference quoted in literature of 33m [18]. As demonstrated in Table S2, there was improvement in WHO FC in all the studies post transitioning from PD5i to riociguat. Mean pulmonary arterial pressure results showed an improvement of 3.14 mmHg (CI 0.80–5.45, p = 0.008) with relative homogeneity as demonstrated by the I^2 of 0% (Fig. 3). PVR also demonstrated an improvement post transition to riociguat of 129 dynes · sec/cm5 (CI 65.0- 193.0, p < 0.001), I^2 = 0% (Fig. 4). CI improved by 0.37l/min/m2 (CI 0.26–0.49, p < 0.00001) (Fig. 5). Other important clinical secondary outcomes such as BNP and RVSP are displayed in Table S2, but due to lack of consistent availability of data across studies, results could not be pooled. Adverse outcomes in the UOHI cohort included new-onset headache in one individual and new symptoms of nausea and presyncope in another. Non-related hospitalization was recorded for 3/11 patients with reasons being pneumonia or rotator cuff tear. In Hoeper et al, 95% of patients reported an adverse effect with four patients (7%) experiencing an adverse event leading to discontinuation of study drug, including right ventricular failure, asthenia, and symptomatic hypotension, of which 2 were study drug related [8]. Two deaths were reported, 1 due to pneumonia and another due subdural hematoma following a traumatic fall; neither were considered drug-related.

Discussion

In this combined meta-analysis encompassing data from a retrospective database study at the UOHI pulmonary hypertension clinic, we summarize the current evidence available on the transition of patients with PAH who fail PDE5i to riociguat. This is the first review to demonstrate there was a clinically important and significant improvement in both clinical outcomes such as 6MWTD and WHO FC as well as hemodynamic factors such as mPAP, PVR and CI post transition. Our review also provided additional information that can be utilized to guide clinicians on which patients can be considered for transitioning to riociguat, the dose titration scheme, washout period, as well as safety considerations.

Pulmonary arterial hypertension is a rare disease associated with significant mortality if untreated [1]. Prior to the advent of current therapies, the median survival of patients was 2.8 years with a quoted 1, 3, and 5-year survival of 68%, 48%, and 34%, respectively [19]. With recent advancements in pharmacologic therapy, the median survival has been extended to greater than 5 years and estimated mean survival is approximately 92%, 74% and 65% at the 1, 3, and 5-year interval, respectively [3]. PDE5i have been a cornerstone of therapy. In previous studies by Galiè and Galiè, sildenafil and tadalafil demonstrated improvement in 6MWTD, quality of life and clinical worsening [20, 21]. However, given the progressive nature of the disease, despite the initial improvement, patients continue to experience clinical worsening.

Riociguat is a more recent therapy with potent pulmonary vasodilation both dependent and independent of NO, offering patients who fail PDE5i an oral option prior to initiation of IV prostanoids. However, due to the rare nature of the disease, it has been difficult to systematically study when and how patients with PAH who fail PDE5i therapy should be transitioned to riociguat. Thus, this is an important study as it is the first meta-analysis targeted at examining transitioning patients from PDE5i therapy to riociguat. Table 1 demonstrates the characteristics of included studies that help to guide clinicians on which patients transitioning to riociguat can be considered, namely in patients who experience clinical deterioration evidence by WHO FC III dyspnea, worsening 6MWTD results or worsening hemodynamic parameters.

Furthermore, this review is also the first to systematically summarize available literature describing how patients were transitioned from PDE5i to (Table 2). Although there were various washout periods used for tadalafil, 24h was the predominant washout period in most studies for sildenafil with no reported adverse outcomes reported relating to an inadequate washout period. There was good agreement across studies in the dose titration scheme, which included starting at 1mg TID with increases of 0.5mg TID every 2 weeks to a maximum of 2.5mg TID or a maximum tolerated dose by the patient. Although adverse effects were not consistently reported, nausea, presyncope due to hypotension and right ventricular failure were the most common reported adverse events that clinicians need to be aware of when transition a patient to riociguat.

Overall, this review demonstrates there was a clinically important and significant improvement in both clinical outcomes such as 6MWTD, WHO FC and hemodynamic factors such as mPAP, PVR and CI. This data demonstrates that patients with limited hemodynamic and clinical benefit on PDE5i can have augmented benefit when they are switched to riociguat.

High heterogeneity between studies and, in general, low quality of included studies represent a significant limitation of this review. Furthermore, there were a variety of primary endpoints across studies, making it challenging to combine the results of the primary literature. Since the completion of the manuscript, a randomized control trial examining the effects of switching to riociguat from PDE5i was published and thus was not included in the analysis [22]. However, results were concordant with the current study, demonstrating switching from PDE5i to riociguat resulted in improvement in a composite clinical of outcome of 6MWD, WHO FC or BNP reduction in patients with PAH at intermediate risk of 1-year mortality [22].

Conclusion

This is the first meta-analysis to comprehensively examine the transition patients with PAH from PDE5i to riociguat in a real-world setting. These results support the transitioning patients on PDE5i with clinical worsening to riociguat, with improvement in both clinical and hemodynamic parameters.

Declarations

Funding: Not applicable

Conflicts of interest/competing interests: Dr. Chandy has participated in clinical trials, advisory boards and speaking engagements with Bayer Pharmaceuticals and Janssen Pharmaceuticals in addition to advisory boards with Apotex Inc. Dr. Mielniczuk has previously received fees for her role as a speaker and consultant for Janssen Pharmaceutical. Dr. Stewart is a founding member, unpaid permanent consultant and equity stakeholder for Northern Therapeutics.

Availability of data & materials: Published data will be publicly available

Code availability: Not applicable

Author contributions:

Kelly Sun penned the local ethics application for approve, performed the extraction of the primary database study data, reviewed articles for final inclusion in the review, performed statistical analysis for the review, drafted the manuscript and made according edits.

Tetyana Kendzerska reviewed articles for final inclusion in the review and quality assessment of included studies, performed statistical analysis of the database study and reviewed the statistical analysis for the review, made edits to the final manuscript.

Julia Foxall submitted the final research ethics application and corresponding corrections and critically reviewed the final manuscript.

Lisa Mielniczuk, Vladimir Contreras and Duncan J. Stewart contributed to the conception and design of this project and critically reviewed the final manuscript.

Carolyn Pugliese contributed to the collection of results for the primary database study and critically reviewed the final manuscript

George Chandy aided in generating the research hypothesis, study design, review of the ethics application, review of the primary database study and review results and critically reviewed the final manuscript.

Ethics approval: The retrospective database study was approved by the Research Ethics Board at the Ottawa Hospital Research Institute.

Consent to participate: Not applicable

Consent for publication: The authors' consent to the publication of the manuscript material

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Tables

Table 1: Characteristics of Included Studies

Author	Type of study	# of patients (n=% female)	Mean Age	Inclusion criteria	Exclusion criteria	Primary endpoint
Hoeper et al.[8]	Multicentre prospective cohort	61 (74)	NA	• Age 18-75 and insufficient response to tadalafil or sildenafil ≥90days, WHO FC III, 6MWTD 165-440cm, CI <3, mPAP >30, PCWP ≤15, PVR >400dyns • First 30 patients had narrower hemodynamic inclusion (CI <2.5 and PVR >480dyn)	• >15% difference in 6MWTD between the 14- day screening period and week 0 • Participated in another clinical trial in the last 30 days • Previously treated with riociguat or prostanoids ≤90 days before baseline • Receiving ongoing therapy with concomitant PDE5i, non-specific phosphodiesterase inhibitors or nitric oxide donors	• Exploratory, no defined primary outcome: • Change from baseline to week 24 in 6MWTD, NT-proBNP, WHO FC, pulmonary haemodynamics and EuroQol 5-Dimensions questionnaire (EQ-5D) score (quality of life) • Proportion of patients experiencing clinical worsening; and safety and tolerability • A combined responder end-point was also assessed • Responders were defined as patients who at week 24 were free from clinical worsening, achieved WHO FC I/II and had a ⩾30 m increase in 6MWTD
Raina et al.[13]	Case series	3 (100)	54	NA	NA	NA
Taran et al.[14]	Single arm pilot study	8 (75)	47	• Idiopathic pulmonary arterial hypertension patients • Patients with inadequate response to sildenafil therapy had at least one of the following criteria at baseline: World Health Organization functional class WHO FC III/IV, 6MWTD <440 m; peak oxygen consumption <15 mL/kg/min; ventilatory equivalents for carbon dioxide >44.9; and inadequate hemodynamic parameters assessed	NA	• Functional class

				by RHC (mPAP >30 mmHg; mean right atrial pressure [mRAP] >8 mmHg; and CI <2.5 L/min/m2).		
Davey et al.[15]	Single centre retrospective cohort	12 (83)	58	• Age 18-80, who are switched from PDE5i to riociguat for treatment of PAH or residual CTEPH after pulmonary thromboendarectomy • Participants were required to have a RHC prior to initiation of PDE5i, repeat RHC and clinical evaluation after mininum of 12 weeks on PDEi and another repeat RHC and clinical evaluation after min 12 weeks on riociguat	NA	• Clinical and hemodynamic changes
Kuroda et al.[16]	Single centre, retrospective cohort	7 (57)	50	• Patients with PAH and CTEPH with: • 1) patients who had dual or triple combination therapy, which included a PDE5i from 2000 to 2017 • 2) patients who experienced side effects caused by a PDE5i, or those who had an inadequate response to combination therapy • 3) WHO FC II or near III and • 4) SBP >100mmHg		• Change in mPAP
Poch[17]	Case study	1 (0)	59	NA	NA	NA
UOHI cohort	Retrospective cohort	11 (55)	58	• Group I pulmonary hypertension as defined by: PVR ≥300dyn-sec-cm^-5 or mPAP ≥25mmHg and PCWP of ≤15mmHg • Patients who had treatment failure on a PDE5 inhibitor defined by: 1) CI <2.5, WHO FC ≥3 or 6MWTD < predicted	• Previous treatment with riociguat	• 6MWTD

Table 2: Pre transition PAH Medications and Riociguat Titration Protocol

Author	Washout periods	Titration protocol	Reason for transition
Hoeper et al. [8]	• Sildenafil: 24h • Tadalafil 72h	• Initiated riociguat at 1mg TID, increased 0.5mg q2weeks	• Insufficient response to PDE5i (no further specifics)
Raina et al. [13]	• Not documented	• Not documented	• Insufficient clinical response
Taran et al. [14]	• Sildenafil: 24h	• Initiated riociguat at 1mg TID, increased 0.5mg q2weeks	• Inadequate response to treatement: patients with inadequate response to sildenafil therapy had at least one of the following criteria at baseline: • World Health Organization functional class (WHO FC) III/IV; 6-minute walking distance (6MWTD) <440 m; peak oxygen consumption (VO2 peak) <15 mL/kg/min; ventilatory equivalents for carbon dioxide (VE/VCO2 slope) >44.9; and inadequate hemodynamic parameters assessed by right heart catheterization (RHC) (mean pulmonary artery pressure [mPAP] >30 mmHg; mean right atrial pressure [mRAP] >8 mmHg; and cardiac index [CI] <2.5 L/min/m2) • The presence of at least one of the above criteria indicated the need for optimizing therapy and the decision to transition patients to riociguat was made by a multidisciplinary group that included both an independent clinician and a member of the study team
Davey et al. [15]	• Not documented	• Not documented	• Clinical worsening in 9 patients, side effects of PDE5i in 1 and approval of riociguat for CTEPH in 2
Kuroda et al. [16]	• Sildenafil: 12h; Tadalafil 24h	• Initiated at 3mg daily dose, protocol not further specified	• Patients who experienced side effects caused by a PDE5i, or those who had no adequate response to combination therapy
Poch[17]	• Sildenafil: no washout	• Initiated riociguat at 1mg TID, increased 0.5mg q2weeks	• Insurance coverage
UOHI	• Sildenafil: 24h • Tadalafil: 48h	• Not documented	• Failure on PDE5i defined by any of: cardiac index less or equal to 2.5, functional class of 3 or greater or 6-minute walk test less than predicted

Figures

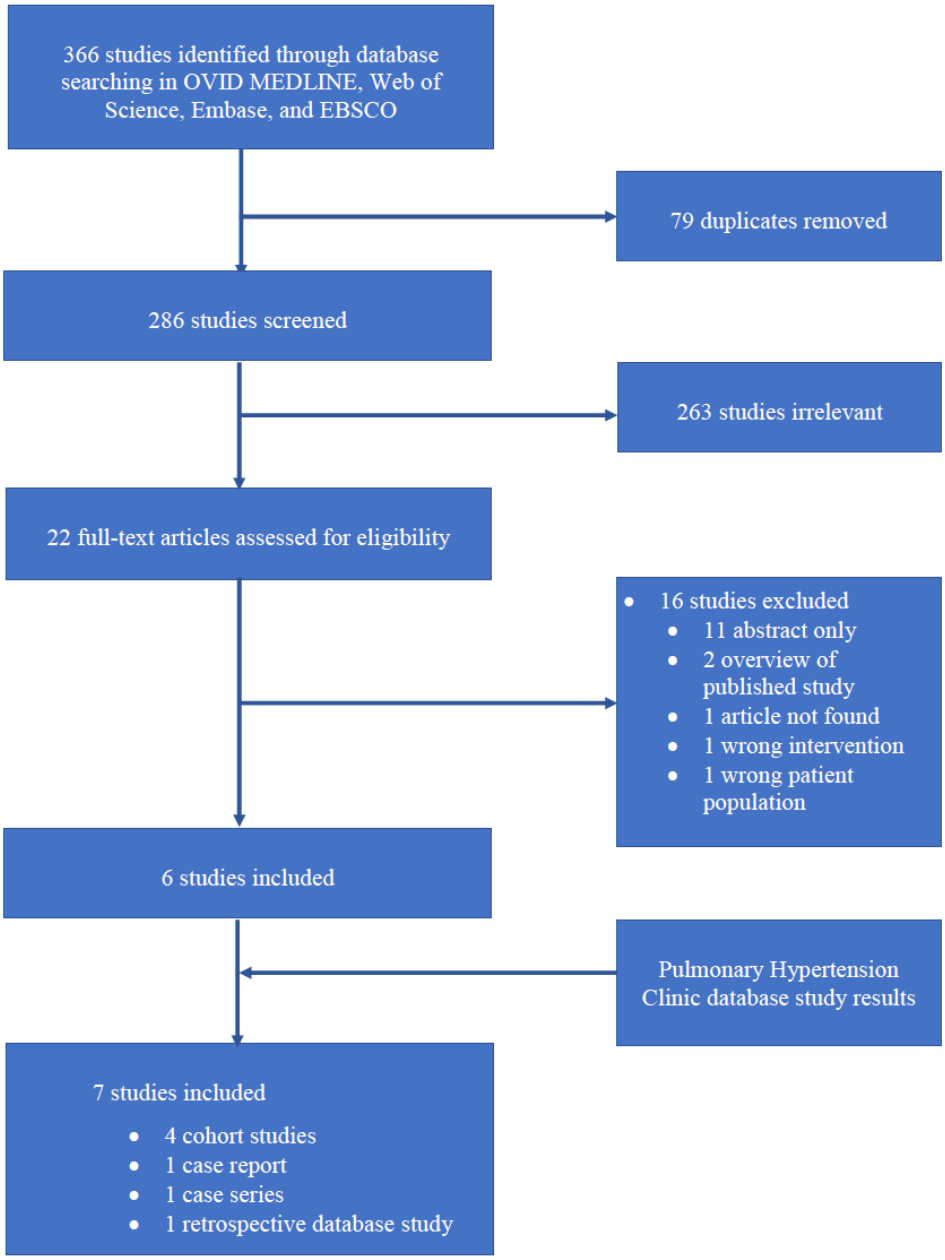
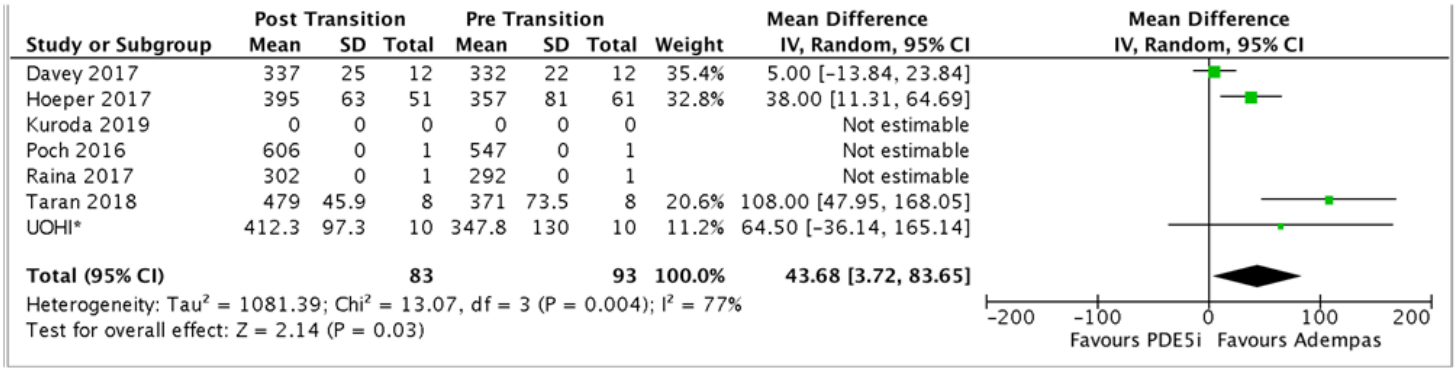


Figure 1

Flow Diagram of Study Selection



Study or Subgroup	Post Transition Mean	SD	Total	Pre Transition Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Davey 2017	337	25	12	332	22	12	35.4%	5.00 [-13.84, 23.84]
Hoeper 2017	395	63	51	357	81	61	32.8%	38.00 [11.31, 64.69]
Kuroda 2019	0	0	0	0	0	0		Not estimable
Poch 2016	606	0	1	547	0	1		Not estimable
Raina 2017	302	0	1	292	0	1		Not estimable
Taran 2018	479	45.9	8	371	73.5	8	20.6%	108.00 [47.95, 168.05]
UOHI*	412.3	97.3	10	347.8	130	10	11.2%	64.50 [-36.14, 165.14]
Total (95% CI)			**83**			**93**	**100.0%**	**43.68 [3.72, 83.65]**

Heterogeneity: Tau² = 1081.39; Chi² = 13.07, df = 3 (P = 0.004); I² = 77%
Test for overall effect: Z = 2.14 (P = 0.03)

Figure 2

Pre and Post Transition to Riociguat 6MWTD Results Increased 6MWTD post transition to riociguat shown by the random-effects model of 43.68m (CI 3.72-83.7, P=0.03, I2=77%) *UOHI: University of Ottawa Heart Institute

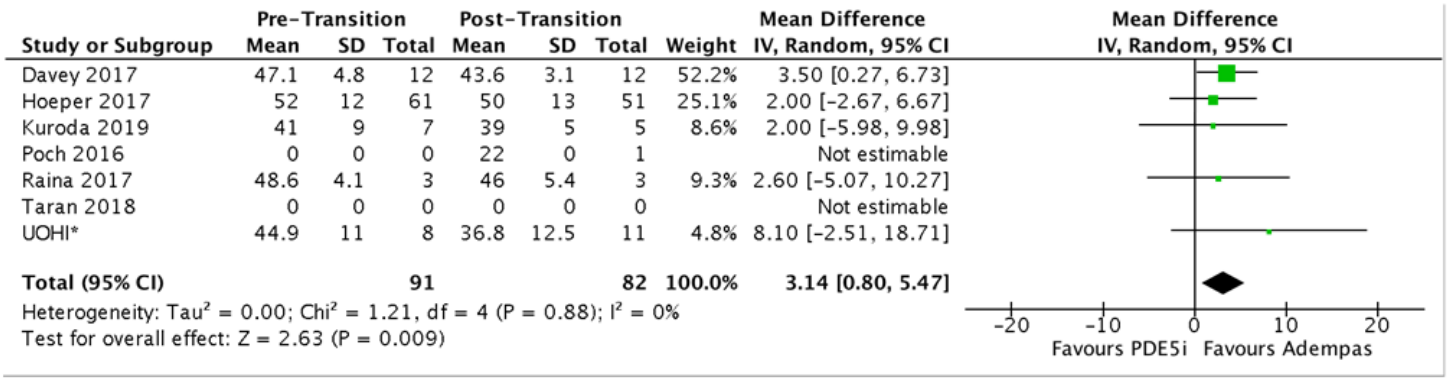


Figure 3

Pre and Post Transition to Riociguat Mean Pulmonary Arterial Pressure Results Increased mPAP post transition to riociguat shown by the random-effects model of 3.14mmHg (CI 0.80-5.47, P=0.009, I2=0%) *UOHI: University of Ottawa Heart Institute

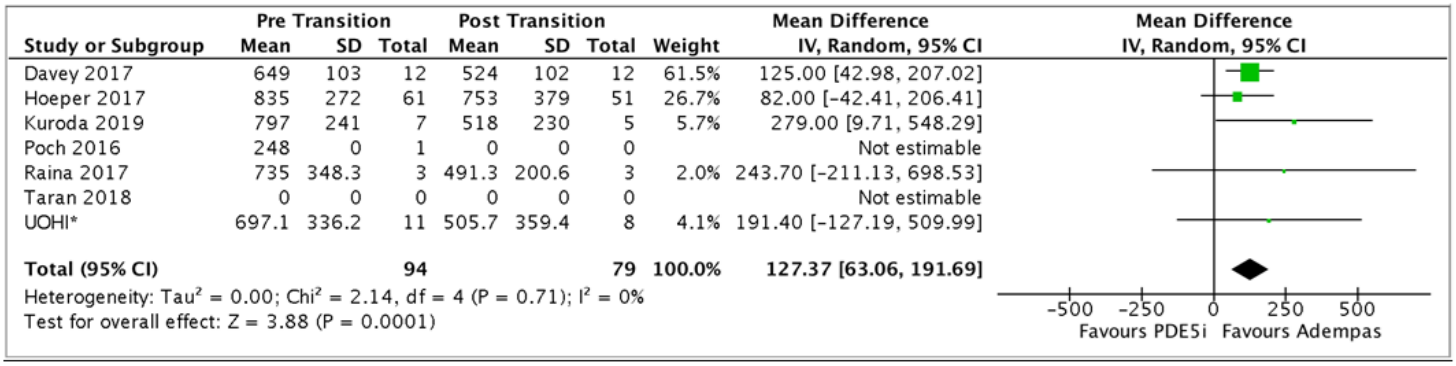


Figure 4

Pre and Post Transition to Riociguat Pulmonary Vascular Resistance Results Increased PVR post transition to riociguat shown by the random-effects model of 127.37 dynes/seconds/cm-5(CI 63.06- 191.69, P=0.0001, I2=0%) *UOHI: University of Ottawa Heart Institute

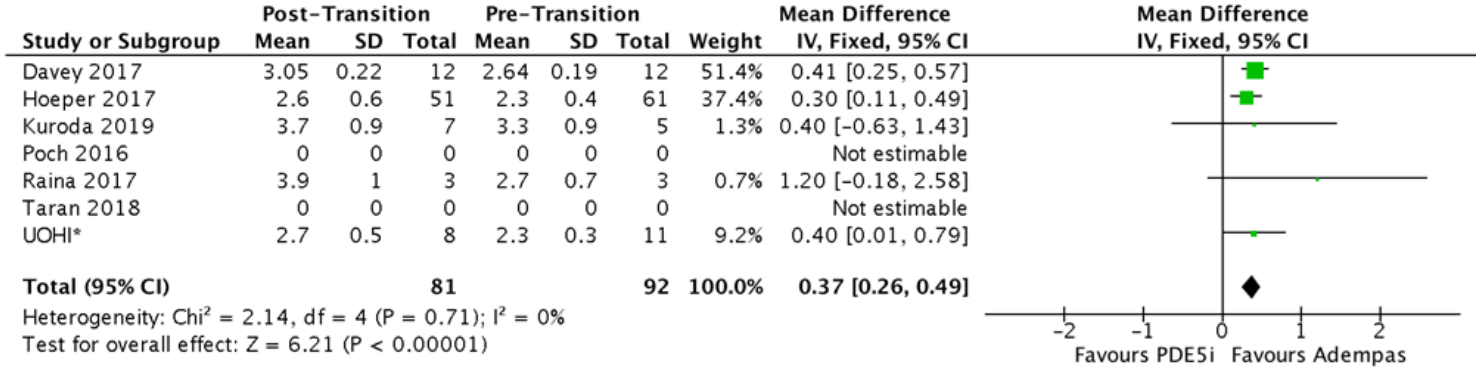


Figure 5

Pre and Post Transition to Riociguat Cardiac Index Results Increased CI post transition to riociguat shown by the random-effects model of 0.37L/min/m2 (CI 0.26-0.49, P<0.00001, I2=0%) *UOHI: University of Ottawa Heart Institute

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- LungSupplementalJuly10.docx