South African National Essential Medicine List
Tertiary Medication Review Process
Component: Circulatory System

TITLE: Evaluation of Phosphodiesterase-5 (PDE5) inhibitors (sildenafil, tadalafil, and vardenafil) in adults with pulmonary arterial hypertension WHO Group 1.

1. Executive Summary

Date: August 2024
Medicine (INN): Phosphodiesterase-5 (PDE5) inhibitors - Sildenafil, Tadalafil, Vardenafil
Medicine (ATC): G04BE03, G04BE08, G04BE09
Indication (ICD10 code): Pulmonary hypertension, WHO Group 1 (I27.0)
Patient population: Adult patients with Pulmonary Arterial Hypertension, World Health Organization (WHO) Group 1
Prevalence of condition: Pulmonary arterial hypertension (PAH) is uncommon compared to other forms of pulmonary hypertension, with an estimated prevalence of 15 to 50 per million.[1]
Level of Care: Tertiary
Prescriber Level: Specialist (pulmonologist/cardiologist)

Key findings

- We conducted a review of the literature to explore the safety and efficacy of PDE5-inhibitors in adults with WHO group 1 pulmonary hypertension.
- A literature search for systematic reviews and meta-analyses meeting the PICO identified 12 citations, and following screening, one systematic review (with meta-analysis) was selected for inclusion: A Cochrane review by Barnes *et.al.*[3]
- PDE5-inhibitors versus placebo:
  - **Six minute walk distance (6MWD)**
    Patients given PDE5-inibibitors could walk further in the 6MWD test than those given placebo; mean difference 48 metres, 95% CI 40 to 56, p <0.001 (8 trials, 880 participants) – moderate certainity of evidence There was significant heterogeneity between trials (I^2 = 51%, p = 0.04) that was not fully explained by the different PDE5-inhbitors used in each trial.
  - **Change in WHO functional class**
    A higher proportion of patients given PDE5-inhibitors achieved an improvement of at least one WHO functional class than those given placebo, OR 8.59, 95% CI 3.95 to 18.72, p < 0.001 (4 studies, 282 participants, I^2= 0%) – high certainity of evidence, however small total sample.
  - **Mortality**
    Patients with group 1 pulmonary arterial hypertension given PDE5-inhibitors had reduced mortality compared to placebo OR 0.22, 95% CI 0.07 to 0.68, i^2=0%, p = 0.009; 8 trials (1119 participants). Number needed to treat (NNT) to previent one death was 32 (95% CI 27 to 78) – low certainty evidence due to concerns with indirectness and imprecision.
  - **Mean pulmonary arterial pressure (mPAP)**
    Larger reduction in mPAP for PDE5-inihibitors compared to placebo, Mean difference was -6.43 mmHg, 95%CI -8.13 to -4.74, p < 0.001, i^2=76% (6 trials, 453 participants) – moderate certainity of evidence, downgrade for inconsistency.
  - **Cardiac index and pulmonary vascular resistance (PVR)**
    Larger increase in cardiac index with use of PDE5-inhibitors compared to placebo, mean difference was 0.28 L/min/m^2, 95% CI 0.16 to 0.40, p < 0.0001, i^2=77% (4 trials, 239 participants) – moderate certainity of evidence reported, downgraded for inconsistency. There was a larger reduction in PVR for PDE5-inhibitors compared to

placebo, mean difference of -4.74 WU, 95% CI -6.13 to -3.35, i^2=44%, p < 0.0001 (3 trials, 266 participants) – high certainty of evidence reported.

- **Quality of life (QoL)**
  Quality of life was assessed in two included studies, however the data was considered too heterogenous to combine. Studies found statistically significant improvements in domains of: physical functioning (p<0.001), general health (p<0.001) and vitality (p<0.05), current health status (p<0.01) and utility index (p<0.01), dyspnoea (p = 0.009) and fatigue (p = 0.04); respectively.
- **Dyspnoea**
  Improvement in dyspnoea reported with use of PDE5-inhibitors compared to placebo, mean difference -0.72, 95% CI -0.99 to -0.44, p<0.001 (4 studies, 239 participants, using Borg scale). However the effect size did not meet the minimum clinical improvement difference; and there was significant heterogeneity across trials (I^2 = 64%, p=0.04).
- **Clinical Worsening**

  Hospitalisation/Change in need for transplant

  - Only three trials (746 participants) reported clinical worsening requiring intervention or hospitalisation. Some included studies reported clinical worsening which included the need for transplant. Although the effect estimate favoured PDE5-inhibitors, there was no statistically significant difference compared to placebo, OR 0.58, 95%CI 0.27 to 1.23, p = 0.16).
- **Adverse events**
  More adverse events in the PDE5-inhibitor groups compared to placebo groups, with statistically significant increases in headache (OR 1.97, 95% CI 1.33 to 2.92; p < 0.001; 5 studies, 848 participants), in gastrointestinal upset (OR 1.63, 95% CI 1.07 to 2.48; p = 0.02; 5 studies, 848 participants), in flushing (OR 4.12, 95% CI 1.83 to 9.26; p < 0.001; 3 studies, 748 participants), and in muscle aches and joint pains (OR 2.52, 95% CI 1.59 to 3.99; p < 0.001; 4 studies, 792 participants). No statistically significant differences were seen for epistaxis, respiratory symptoms, or visual disturbance.

➡ There are no head-to-head studies of sildenafil, tadalafil and vardenafil, however all show a beneficial direction of effect.

➡ **Recommendation:** *The Tertiary/Quaternary Expert Review Committee suggest the use of PDE5-inhibitors in adult patients with WHO Group 1 Pulmonary Arterial Hypertension.*

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: The Tertiary and Quaternary Expert Review Committee suggest the use of PDE5-inhibitors in adults with pulmonary arterial hypertension, WHO Group 1. It is recommended that the PDE5-inhibitors: sildenafil, tadalafil and vardenafil be considered a therapeutic class for this indication with the most affordable agent procured.

Rationale: Compared to placebo, the PDE5-inhibitors show statistically significant benefits in mortality, 6-minute walk distance, WHO functional class, and haemodynamic parameters. There were however considerable limitations in mortality assessment (indirectness and imprecision) and thus the true effect on mortality is unknown. Although there are more adverse effects associated with PDE5-inhibitor therapy, these do not outweigh the potential benefits. All three PDE5-inhibitors assessed were included in the meta-analysis and were shown to be efficacious for this indication.

Level of Evidence: High quality systematic review, with low to high GRADED certainty of evidence.
Review indicator: New high-quality evidence of a clinically relevant benefit/safety concerns

NEMLC RECOMMENDATION: Notwithstanding the abovementioned data limitations, NEMLC recommended the inclusion of PDE5 inhibitors in adults with WHO group 1 PAH (August 2024).
Monitoring and evaluation considerations:
Research priorities:

Summary of findings table: Group 1 Pulmonary arterial hypertension: PDE5-inhibitors versus placebo

Group 1 Pulmonary arterial hypertension - PDE5i compared to placebo

Patient or population: people with pulmonary arterial hypertension
Setting: outpatients
Intervention: PDE5 inhibitors
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with PDE5i				
Improvement in WHO functional class	61 per 1000	358 per 1000 (204 to 549)	OR 8.59 (3.95 to 18.72)	282 (4 RCTs)	⊕⊕⊕⊕ HIGH	-
Six-minute walk distance	Ranges from 170 - 319 m[a]	MD 48 metres higher (40 higher to 56 higher)	-	880 (8 RCTs)	⊕⊕⊕◯[b] MODERATE	6MWD in PAH MCID is 41 metres
Mortality	41 per 1000	9 per 1000 (3 to 28)	OR 0.22 (0.07 to 0.68)	1119 (8 RCTs)	⊕⊕⊕⊕ HIGH	-
Quality of life SF-36: (scores 1 to 100, higher scores indicate better QoL) EQ-5D questionnaire: (higher scores indicate worse QoL) CHFQ: (lower scores indicate worse QoL)	Galiè 2005a found a statistically significant improvement in all SF-36 domains for sildenafil-treated participants, and when compared to placebo in physical functioning (P < 0.001), general health (P < 0.001), and vitality (P < 0.05). There was also a statistically significant improvement in placebo-treated participants in the physical functioning domain. Galiè 2005a found statistically significant improvements for the EQ-5D current health status (P < 0.01) and utility index (P < 0.01). Sastry 2004 found a statistically significant difference for the CHFQ fatigue domain (sildenafil post-treatment score 22.33, SD 4.82 compared to placebo post-treatment score 20.67, SD 5.19; P = 0.04), and a non-statistically significant difference in the emotional function domain (sildenafil post-treatment score 37.33, SD 9.3, compared to placebo post-treatment score 34.71, SD 10.91; P = 0.06), favouring sildenafil compared with placebo.			163 (2 RCTs)	-	Data considered too heterogeneous to meta-analyse
PAP	-	MD 6.43 mmHg lower (8.13 lower to 4.74 lower)	-	453 (6 RCTs)	⊕⊕⊕◯[b] MODERATE	The higher the mean PAP, the worse the PH
RAP	-	MD 1.35 mmHg lower (2.34 lower to 0.36 lower)	-	341 (3 RCTs)	⊕⊕⊕⊕ HIGH	The higher the RAP, the worse the PH
Cardiac index	-	MD 0.28L/min/m^2 higher (0.16 higher to 0.4 higher)	-	239 (4 RCTs)	⊕⊕⊕◯[b] MODERATE	The lower the cardiac index, the worse the PH
PVR	-	MD 4.74 WU lower (6.13 lower to 3.35 lower)	-	266 (3 RCTs))	⊕⊕⊕⊕ HIGH	The higher the PVR. the worse the PH

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

6MWD: six-minute walk distance; **CI:** Confidence interval; **EQ-5D**: EuroQoL 5D; **MCID:** minimal clinically important difference; **MD**: mean difference; **OR:** odds ratio; **PAP**: pulmonary arterial pressure; **PDE-5i:** phosphodiesterase-5 inhibitor; **PH**: pulmonary hypertension; **PVR**: pulmonary vascular resistance; **RAP**: right atrial pressure; **RCT**: randomised controlled trials; **SD**: standard deviation; **SF-36**: Medical Outcomes Study 36-item short form; **WU**: woods units; **WHO**: World Health Organization

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Post-treatment values for participants in the placebo group were presented in two studies only; the remaining included studies presented a mean difference only.
[b]Downgraded due to imprecision owing to significantly high heterogeneity, although the direction of effect is consistent.

2. Name of author(s)/motivator(s):

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- Kim MacQuilkan
- Derusha Frank
- Roger Wiseman
- Marc Blockman

3. Author affiliation and conflict of interest details

» Jane Riddin (Essential Drugs Programme) has no interests to declare
» Kim MacQuilkan (EpiC-SCTA) has no interests to declare
» Derush Frank (CHAI) has no interests to declare
» Roger Wiseman (Liberty Health (Pty) Ltd, South Africa) has no interests to declare.
» Marc Blockman (Department of Clinical Pharmacology, Groote Schuur Hospital, Cape Town, Western Cape, South Africa and the Department of Medicine, University of Cape Town, Cape Town, Western Cape, South Africa). Has no interests to declare.

4. Introduction/ Background

Pulmonary hypertension refers to a group of conditions defined by a mean pulmonary artery pressure ≥ 25 mmHg at rest on right-heart catheterisation. The World Health Organization (WHO) has classified pulmonary hypertension into five groups based on the underlying mechanisms. This review will explore WHO group 1 pulmonary arterial hypertension (PAH).[2]

Group 1 PAH occurs in settings of increase pulmonary vascular resistance. The availability of therapies targeting the pulmonary arterial bed have led to improvements in a condition that previously had an extremely poor prognosis.[2,3]

Phosphodiesterase type 5 inhibitors reduce cyclic guanosine monophosphate (cGMP) degrading enzyme activity, which increases cGMP production. [3]

Nitric oxide, a pulmonary vasodilator is an expensive gas that requires administration via ventilation with a specialised machine at a certain dose to obtain efficacy without developing adverse effects. PDE5-inhibitors thus offer a potential advantage in this indication as they are less costly, and more practical in terms of method of administration.

5. Purpose/Objective (PICO):

Population:	Adults with Primary Arterial Hypertension (WHO Group 1)
Intervention:	PDE5-inhibitors
Comparators:	Placebo
Outcomes:	• Mortality, • hospitalisations; • 6 Minute Walk Test (6MWD); • WHO functional class; • mean pulmonary arterial pressure (mPAP), • Pulmonary Vascular Resistance (PVR) and cardiac index. • Change in need for transplant. • quality of life/health status, • dyspnoea, • clinical worsening (hospitalisation/intervention), • adverse events.
Study types	Systematic reviews, meta-analyses

Methods:

a. Search strategy

A literature search was conducted in PubMed, and the Cochrane Library using above PICO (See Appendix 2).

b. Study selection

Abstract and title screening was undertaken in duplicate independently by JR and KM, with conflicts resolved through discussion. Twelve systematic reviews were identified for consideration, and following title and abstract screening, three were recommended for full text review. Two systematic reviews were Cochrane reviews evaluating the same question (initial and update). The older record was excluded and only the latest version was considered for inclusion. The two remaining studies: Barnes *et.al.*[3] and Shi *et.al.*[4] underwent full text review and AMSTAR assessment (in duplicate by DF and JR), and consideration for inclusion was discussed with the Tertiary Expert Review Committee. Shi *et.al.* was recommended to be excluded due to critically low AMSTAR II assessment, as well as inclusion of non-randomised trials. *(See PRISMA diagram below)*

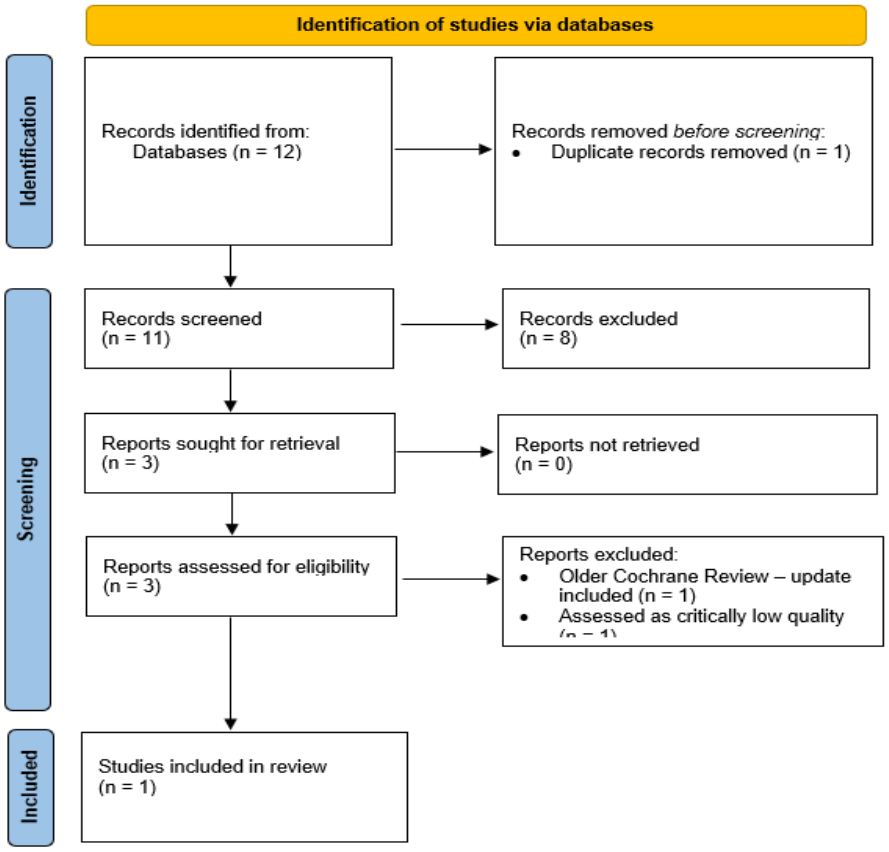

Figure 1: PRISMA diagram

c. Data extraction, management, analysis and quality assessment

Data extraction was undertaken by one reviewer (JR) and checked by a second reviewer (DF or KM)

d. Excluded studies:

Author, date	*Type of study*	*Reason for exclusion*
Shi et.al. 2022	Systematic review and meta-analysis of randomized and non-randomised studies	• AMSTAR II score – Critically low quality. • Included both randomised and non-randomised trials. • Limited to only Asian patients

e. Evidence synthesis:

Author, date	*Type of study*	N	Population	Comparators	Primary outcome	Effect sizes	Comments
Barnes et.al. 2019	Systematic Review and meta-analysis (Cochrane)	36 Studies (RCTs) (2999 participants) [19 trials included patients with group 1, 11 of which compared PDE5-inhibitors to placebo)	Individual with a diagnosis of pulmonary hypertension from any cause who required medical treatment	PDE5-inhibitors vs Placebo or other treatment used for pulmonary hypertension. Of 11 trial comparing PDE5-inhibitors to placebo: • 7/11 evaluated sildenafil • 3/11 evaluated tadalafil • 1/11 evaluated vardenafil	• Change in WHO functional class • 6MWD • Mortality	<u>Change in WHO functional Class:</u> • OR 8.59 (95%CI 3.95 to 18.72) (HIGH certainty of evidence) <u>6MWD</u> • Mean difference 48 meters higher. (41 meters considered minimum clinically important difference - MODERATE certainty) <u>Mortality</u> • OR 0.22 (95% 0.07 to 0.68) (HIGH certainty)	AMSTAR: High Quality

Assessment of methodological quality

AMSTAR 2 assessment on Barnes et.al. (performed in duplicate JR and DF) found it to be of high quality.

Risk of Bias and certainty of evidence

The SR conducted Risk of Bias 1 assessments on the included studies and reported that most studies had low risk of bias, with the direction of effect consistent across them (See figure 2 below). Certainty of evidence was not downgraded due to high risk of bias for any the outcomes reported in this medicine review. The outcomes of mortality and change in WHO functional class both were GRADED as high certainty, with the outcomes of 6MWD, mPAP and CI downgraded to moderate certainty due to high heterogeneity. However, it is important to note that there are some weaknesses in the included studies for the WHO Group 1 assessment, including small sample sizes and one study only evaluating children which was not published in full. In this regard the GRADE evaluation of high certainty of evidence for mortality was downgraded to low due to indirectness (study with only children included) and imprecision (removal of that one study will likely result in the CI crossing the line of no effect).

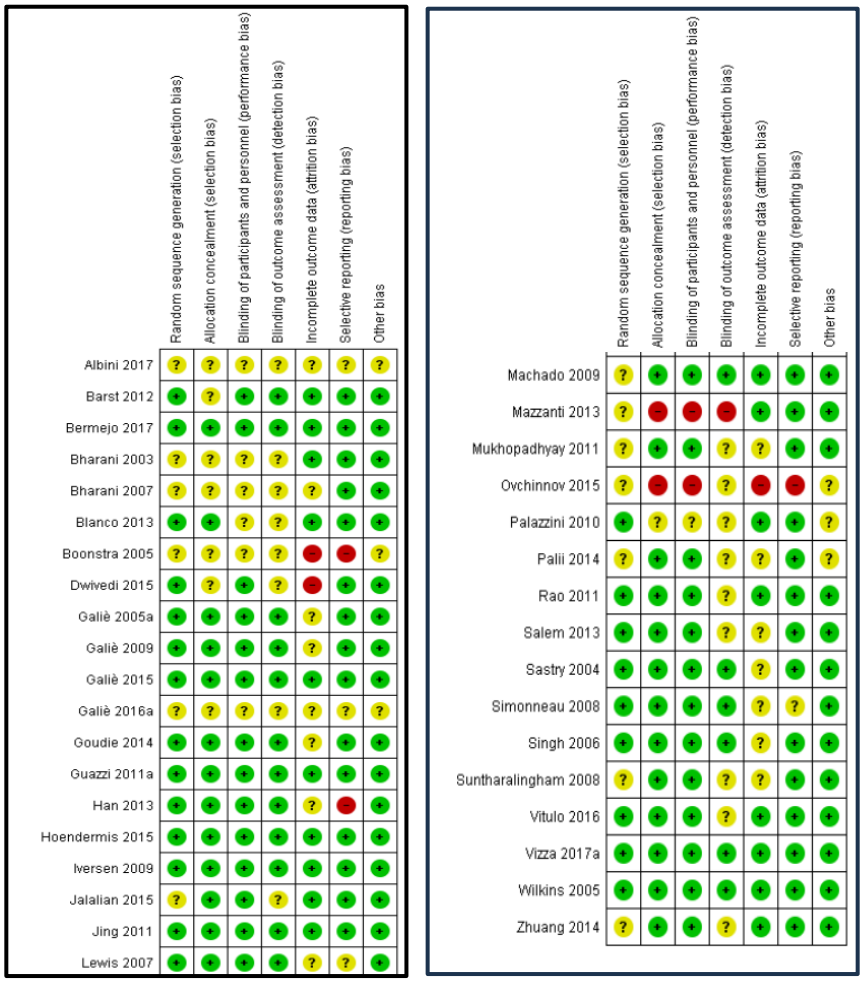

Figure 2: Most studies had low risk of bias, with the direction of effect consistent across them.

Effects of intervention

Comparison 1: PDE5-inhibitors versus placebo

Outcome 1.1: Mortality

There were less deaths with use of PDE5-inhibitors as compared to placebo in patients with group 1 pulmonary arterial hypertension; OR 0.22, 95%CI 0.07 to 0.68, i^2=0%, p = 0.009; 8 trials (1119 participants) - high certainity of evidence reported (See Summary of Findings Table). Number needed to treat (NNT) to previent one additional death was 32 (95% CI 27 to 78). See figure 3 and 4 below. To note that the estimates for tadalafil and vardenafil did cross the null however all results were in the same direction (in favour of the agent) and no difference was observed betwewen agents in the test for subgroup differences (i^2=0%, P=0.66). Samples sizes were also smaller, in particular for vardenafil. It is important to note that the study by by Palii et.al. which appears to show the biggest benefit was not published in full, and was limited to paediatric patients. If this study was to be removed from the analysis it is likely that the benefit seen for sildenafil over

placebo is not statistically significant. In light of this, certainity of evidence is downgraded from high to low for indirectness (childen) and imprecision.

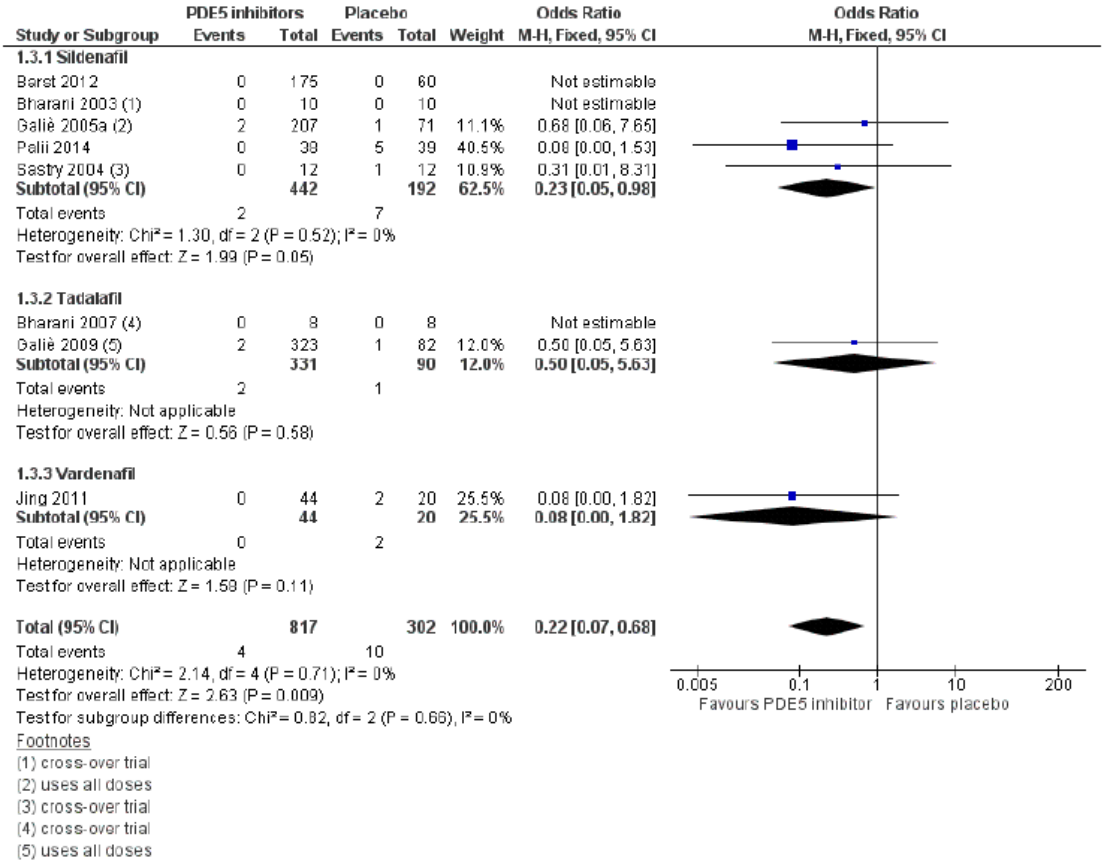

Figure 3: Forest plat of comparison 1.1 Group 1 pulmonary arterial hypertension – PDE5-inhibitors versus placebo, outcome: MORTALITY

Figure 4: Cates plot for mortality with PDE5-inhibitors treatment in group 1 pulmonary arterial hypertension

Outcome 1.2: Hospitalisation

This outcome was not specifically reported on – See Outcome 1.10 Clinical Worsening.

Outcome 1.3: Six minute walk distance (6MWD)

There was a statistically significant improvement in 6MWD with PDE5-inibibitors compared to placebo; mean difference 48 metres, 95% CI 40 to 56, p <0.001 (8 trials, 880 participants). Moderate certainity of evidence reported, downgraded due to significant heterogeneity between trials (I^2 = 51%, p = 0.04) that was not fully explained by different PDE5-inhibitors used in each trial. It was reported that the effect was clinically significant, with the mean difference observed being larger than 41 metre point sourced from literature (Gilbert 2009[5]). *See figure 5* and Summary of Findings Table).

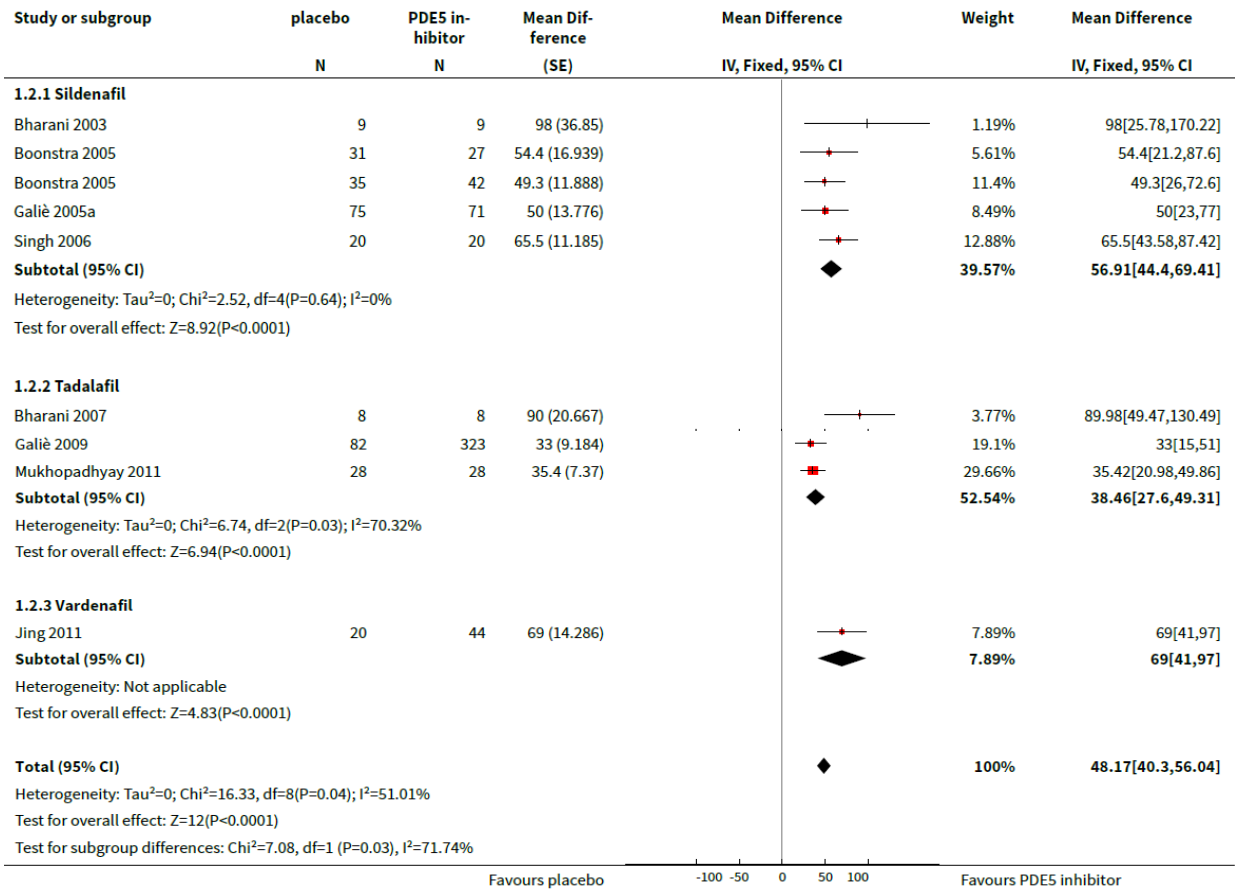

Figure 5: Forest plot: Group 1 pulmonary arterial hypertension – PDE5-inhibitors versus placebo, outcome: 6MWD

Outcome 1.4: Change in WHO functional class

More participants with a reported improved change in WHO functional class in the PDE5-inhibitors group compared to placebo, OR 8.59, 95% CI 3.95 to 18.72, p < 0.001, I^2= 0% (4 studies, 282 participants) – High certainity of evidence reported. See Figure 6 and Summary of Findings Table). Similarly to mortality, the estimates for tadalafil and vardenafil did cross the null however all results were in the same direction (in favour of the agent) and no difference was observed betwewen agents in the test for subgroup differences (i^2=0%, P=0.86). Samples sizes were also smaller, in particular for vardenafil.

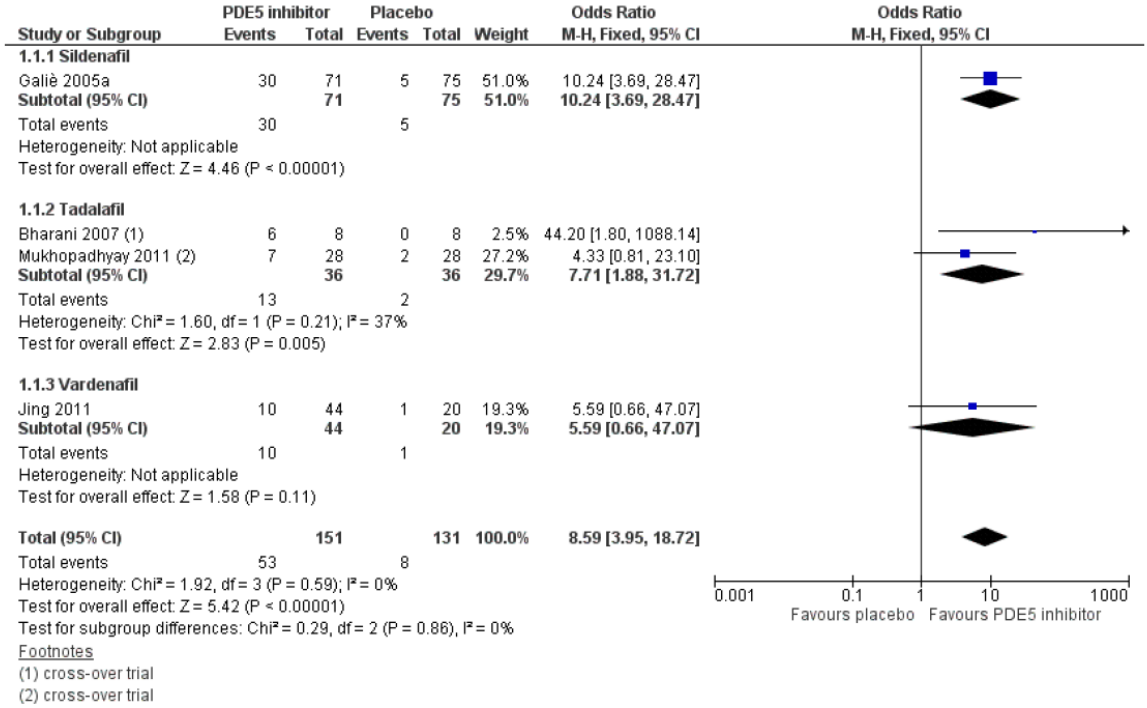

Figure 6: Forest plot: Group 1 pulmonary arterial hypertension – PDE5-inhibitors versus placebo, outcome: IMPROVEMENT IN WHO FUNCTIONAL CLASS

Outcome 1.5: mean pulmonary arterial pressure (mPAP)

There was a larger reduction in mPAP for PDE5-inhibitor participants compared to those on placebo, Mean difference was -6.43 mmHg, 95% CI -8.13 to -4.74, p < 0.0001, i=76%, (6 trials, 453 participants) – moderate certainity of evidence reported, downgraded for due to heterogeinity. The test for subgroup difference between agents was not significant (P = 0.23; I^2 = 31%) and direction of effect was the same although estimates for tadalafil and vardenafil did cross the null.

Outcome 1.6: Cardiac index and PVR

There was a larger improvement in cardiac index with use of PDE5-inhibitors compared to placebo, mean difference was 0.28 L/min/m^2, 95% CI 0.16 to 0.40, p < 0.0001, i^2=77% (4 trials, 239 participants) – moderate certainty of evidence reported, downgraded due to heterogeneity. Heterogeneity was reportedly likely due to the difference between agents (test for subgroup difference i^2=82%), and the estimate for tadalafil crossed the null however estimates for both sildenafil and vardeniful did not.

There was a larger reduction in PVR for PDE5-inhibitors compared to placebo, mean difference of -4.74 WU, 95% CI -6.13 to -3.35, p < 0.0001, i^2=44% (3 trials, 266 participants - high certainty of evidence reported). Results were favourable for all agents, with no difference observed between them (i^2=44%, P=0.17).

Outcome 1.7: Change in need for transplant

This outcome was not specifically reported – See Outcome 1.10 Clinical Worsening.

Outcome 1.8: Quality of life (QoL)

Quality of life was assess in two included studies, however the data was considered too heterogenous to combine for meta-analysis. One trial (Galiè *et.al*.[6]) assessed QoL using 2 measures, SF-36 (medical outcomes Study 36-item short form) and the EuroQoL 5D questionnaire. Statistically significant improvements were found in all domains with SF-36: physical functioning (p<0.001), general health (p<0.001) and vitality (p<0.05). EuroQoL assessment also found statistically significant improvements for current health status (p<0.01) and utility index (p<0.01).

A study by Sastry *et.al*.[7] assessed QoL using the chronic heart failure questionnaire which includes domains on dyspnoea, fatigue and emotional function. Statistically significant improvements in those on sildenafil were found for both dyspnoea (p = 0.009) and fatigue (p = 0.04); however no statistically significant changes were see for the emotional function domain (p =0.06).

Outcome 1.9: Dyspnoea

An improvement in dyspnoea in favour of of PDE5-inhibitors was observed compared to placebo, mean difference was -0.72, 95% CI -0.99 to -0.44, p<0.001 (4 studies, 239 participants, using Borg scale). However the effect size did not meet the minimum clinical improvement difference; and there was significant heterogeneity across trials (I^2 = 64%, p 0.04). The test for subgroup differences between agents suggested that other factors may be the cause besides the difference between agents (I^2 = 37%; P = 0.20).

Outcome 1.10: Clinical Worsening

Only three trials (746 participants) reported clinical worsening requiring intervention (including need for transplant) or hospitalisation. Although the effect estimate favoured PDE5-inhibitors, the estimate crossed the null, OR 0.58, 95%CI 0.27 to 1.23, i^2=0%, p = 0.16).

Outcome 1.11: Adverse events

Generally, there were more adverse events in the PDE5-inhibitor groups compared to placebo groups, with statistically significant increases in headache (OR 1.97, 95% CI 1.33 to 2.92; p < 0.001, i^2=0%; 5 studies, 848 participants), in gastrointestinal upset (OR 1.63, 95% CI 1.07 to 2.48; p = 0.02, i^2=57%; 5 studies, 848 participants), in flushing (OR 4.12, 95% CI 1.83 to 9.26; p < 0.001, i^2=0%,; 3 studies, 748 participants), and in muscle aches and joint pains (OR 2.52, 95% CI 1.59 to 3.99; p < 0.001, i^2=56%; 4 studies, 792 participants).

No statistically significant differences were seen for epistaxis, respiratory symptoms or visual disturbance.

Costs

Table 1: Per patient costs based on single exit prices (most affordable generic) for most appropriate strength

	Dose	Tablet strength (mg)	Cost per day*	Cost per week	Cost per month
Sildenafil	20mg 8 hourly	20	R41.13	R287.91	R1,151.64
Tadalafil	20 mg daily	20	R35.75	R250.25	R1,001.00
Vardenafil	5mg 12 hourly	5	R91.44	R640.08	R2,560.32

**Prices based on most affordable Single Exit Price (SEP): SEP database April 2024 (sildenafil and tadalafil – Macleods product, vardenafil – Bayer product)*

More affordable generics are available for other strengths of these products. See below – if dosing is changed for sildenafil, and tablets are halved, and if vardenafil tablets are halved – costs can be decreased.

Table 2: Per patient costs based on single exit prices (most affordable generic)

	Dose	Tablet strength (mg)	Cost per day	Cost per week	Cost per month
Sildenafil	25mg 8 hourly	50	R25.41	R177.84	R711.36
Tadalafil	20 - 40 mg daily	20	R35.75	R250.25	R1,001.00
Vardenafil	5mg 12 hourly	10	R21.04	R147.30	R589.21

Based on a prevalence of PAH of around 15 to 50 cases per million, it can be postulated that there would be 900 to 3000 cases in South Africa. This would result in a monthly budget impact of approximately 1 to 3 million rand.

Conclusion

The evidence of benefit of PDE5-inhibitors (sildenafil/tadalafil/vardenafil) compared to placebo in patients with WHO group 1 PAH in terms of outcomes of mortality, 6MWD, change in WHO functional class and haemodynamic parameters ranged from low to high certainty. Although evidence for improvement in quality of life is not robust, there also appears to benefit in this domain as well. Adverse effects with use of PDE5-inhibitors are greater as compared to placebo, however these do not outweigh the potential benefits.

There are no head-to-head studies comparing the various PDE5-inhibitors, however the direction of beneficial effect was observed for all PDE-inhibitors included in the review (sildenafil, tadalafil and vardenafil) although estimates for tadalafil and vardenafil did cross the line of no effect for some outcomes and subgroup differences were reported. Samples sizes and number of studies tended to be smaller for those two agents which may have been a limitation. The direction of effect however was the same for all outcomes. Thus, it is proposed that the PDE5-inhibitors be considered a therapeutic class for this indication.

The Tertiary and Quaternary ERC recommends the inclusion of PDE5-inhibitors on the essential medicines list for the indication of WHO group 1 pulmonary arterial hypertension.

Appendix 1: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the quality of evidence?** High [X] Moderate [ ] Low [ ] Very low [ ] **What is the certainty of evidence?** High [X] Moderate [X] Low [X] Very low [ ]	Quality: AMSTAR II assessment – High quality Certainty of evidence GRADED outcomes: **Mortality** = High certainty of evidence specified in the systematic review, but reassessment by reviewers downgraded to **Low certainty** of evidence for indirectness and imprecision (inclusion of study only on children, and exclusion of this study may render result not statistically significant). Potentially, could also be downgraded for concerns with risk of bias or publication bias due to lack of full text availability. **6MWD, Cardiac Index and PAP** = **Moderate** certainty of evidence **WHO functional Class and PVR** = **High** certainty of evidence
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [X] Small [X] None [X]	Moderate or small • Mortality = NNT 32 (95% CI 27 to 78) • 6MWD = MD 48 metres (95% CI 40m to 56m) • Change in WHO functional class = OR 8.59 (95% CI 3.95 to 18.720 – need to work out NNT from forest plots • mPAP = MD -6.43mmHg (95% CI -8.13 to -4.74) • Cardiac Index = MD 0.28 L/min/m2 95% CI [0.16 to 0.40] • PVR = MD-4.74 WU 95% CI [-6.13 to -3.35] None • Dyspnea didn't meet clinical criteria for improvement

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [ ] Moderate [X] Low [ ] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	*Certainty of evidence not reported for adverse events*
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge [ ] Moderate [X] Small [ ] None [ ]	Statistically significant increases in adverse effects were reported for headache, gastrointestinal upset, flushing, as well as muscle aches and joint pains. In the context of the mortality benefit associated with the PDE-5 inhibitors, these adverse effects were not deemed to outweigh the associated benefits.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [X] Favours control [ ] Intervention = Control *or* Uncertain [ ]	Although the adverse events were greater in PDE5-inhibitor group, the beneficial effects, especially in terms of mortality were deemed to outweigh the risks.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [X] No [ ] List the members of the group. Sildenafil Tadalafil Vardenafil List specific exclusion from the group: Nil	Recommended that PDE5-inhibitors be considered a therapeutic class with agents: sildenafil, tadalafil and vardenafil included.
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive [X] Less intensive [ ] Uncertain [ ]	See cost tab – PDE5-inhibitor costs would be additive to current care
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [X] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	
EQUITY	**Would there be an impact on health inequity?** Yes [X] No [ ] Uncertain [ ]	Access on the EML will allow all hospitals managing these patients to access this care.

Appendix 2: Search Strategy

PubMed

Search	Query	Search Details	Results
#3	Pulmonary hypertension AND PDE5-inhibitors AND Meta-analysis/Systematic reviews AND Adult population NOT erectile dysfunction.	(("hypertension, pulmonary"[MeSH Terms] AND ("sildenafil citrate"[MeSH Terms] OR "tadalafil"[MeSH Terms] OR "vardenafil dihydrochloride"[MeSH Terms] OR "phosphodiesterase inhibitors"[MeSH Terms])) NOT "erectile dysfunction"[MeSH Terms]) AND ((meta-analysis[Filter] OR systematicreview[Filter]) AND (alladult[Filter]))	8
#2	Pulmonary hypertension AND PDE5-inhibitors AND Meta-analysis/Systematic reviews AND Adult population	(("hypertension, pulmonary"[MeSH Terms] AND "sildenafil citrate"[MeSH Terms]) OR "tadalafil"[MeSH Terms] OR "vardenafil dihydrochloride"[MeSH Terms] OR "phosphodiesterase inhibitors"[MeSH Terms]) AND ((meta-analysis[Filter] OR systematicreview[Filter]) AND (alladult[Filter]))	76
#1	Pulmonary hypertension AND PDE5-inhibitors AND Meta-analysis/Systematic reviews	(("hypertension, pulmonary"[MeSH Terms] AND "sildenafil citrate"[MeSH Terms]) OR "tadalafil"[MeSH Terms] OR "vardenafil dihydrochloride"[MeSH Terms] OR "phosphodiesterase inhibitors"[MeSH Terms]) AND (meta-analysis[Filter] OR systematicreview[Filter])	366

Cochrane Library

search	Query	Results
#1	MeSH descriptor: [Sildenafil Citrate] explode all trees	1184
#2	MeSH descriptor: [Vardenafil Dihydrochloride] explode all trees	200
#3	MeSH descriptor: [Tadalafil] explode all trees	609
#4	MeSH descriptor: [Phosphodiesterase 5 inhibitors] explode all trees	538
#5	MeSH descriptor: [Hypertension, Pulmonary] explode all trees	1689
#6	#5 AND(#1 OR #2 OR #3 OR #4)	304
#7	#6 PLUS Cochrane review limit	4

Search summary

	Findings
Pubmed	8
Cochrane	4
Duplicates removed	1
Total summary	11

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