Effect of Metformin on Left Ventricular Mass and Functional Parameters in Non-Diabetic Patients: A Meta -analysis of Randomized Clinical Trials

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Appendix 3: Risk of Bias assessment in theEffect of Metformin on Left Ventricular Ejection Fraction (LVEF)

Unique ID	LVMI-Mohan	**Study ID**	Mohan 2019	**Assessor**	Ahmed
Ref or Label	2	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Metformin	**Comparator**	Placebo	**Source**	Journal article(s)
Outcome	LVEF	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Randomization was carried out by Tayside Pharmaceuticals using a validated block randomization method (www.randomization.com). The IMP supply was sequentially numbered and the randomization key held in sealed envelopes by Tayside Pharmaceuticals, Ninewells Pharmacy.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	The investigating team did not have access to the key until after analysis had taken place
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	N	DB-RCT The investigating team did not have access to the key until after analysis had taken place
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NA	
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	Drop out rates were similar across groups
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	Drop out rates were similar across groups
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Data analyzed using miTT and per-protocol and similar results were found
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	DB-RCT and the protocol and method of assessment were pre-specified
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	The protocol and method of analysis were published and no deviations occured
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	Change from baseline was defined a priori

reported result	5.3 ... multiple eligible analyses of the data?	N	Change from baseline only
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	LVMI-Larsen	**Study ID**	LVMI-Larsen	**Assessor**	Ahmed
Ref or Label	3	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Metformin	**Comparator**	Placebo	**Source**	Journal article(s)
Outcome	LVMI	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	The unequal treatment assignment (19vs. 17 patients) was due to a pre-established computer-generated sequence equally balanced at 40 patients to account for dropouts.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PN	
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PN	Dropout rates were similar
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	Dropout rates were similar
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N	Pill count showed good compliance
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Y	ITT used
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	All 36 patients initially randomized were analysed
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	DB-RCT
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	DB-RCT
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	

Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	a total of 36 patients were required to detect a relative WMI difference of 0.6 mL·mmHg·m−2·106 between the two treatment groups (a 2-sided ?? of 0.05 at 80% power) while allowing for 17% dropout. Data
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	LVMI-Sardu	**Study ID**	Sardu 2021	**Assessor**	Ahmed
Ref or Label	6	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Metformin	**Comparator**	Placebo	**Source**	
Outcome	LVMI	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	PY	The authors used a computer-generated randomization scheme, and the randomization was performed by calling the IVRS. Finally, the medications were dispensed using bottle numbers assigned by the IVRS.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PN	Double blinded
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NA	
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	All patients were analyzed
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	The examination was performed at baseline and after 12 months, according to the American Society of Echocardiography recommendations
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	

Bias in selection of the reported result	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	LVMI-Velázquez	**Study ID**	Velázquez 2015	**Assessor**	
Ref or Label	7	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Metformin	**Comparator**	SOC	**Source**	
Outcome	LVMI	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	PN	Not indicated
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	All were comparable
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	No placebo
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	Y	
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	No, objective measurment
	4.3 Were outcome assessors aware of the intervention received by study participants?	PY	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	No specified protocol. However, no direct comparison between groups
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	

	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	LVMI-Ali	**Study ID**	Ali 2016	**Assessor**	Ahmed
Ref or Label	8	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Metformin	**Comparator**	Placebo	**Source**	Journal article(s)
Outcome	LVMI	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Block randomization. Manufacturing and packaging including blinding wasperformed by Stichting Apotheek Haagse Ziekenhuizen, DenHaag, the Netherlands, according to the Good Manufacturing Practice standards of the European Union
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PN	Double blinded randomized RCT
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NA	
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	A total of 380 patients were randomized. However, only ~140 completed the study.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	LVEF values were imputed in the original study and results did not differ
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PN	Double blinded and missing proportions were similar across groups. Reasons for missingness were also indicated
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Echocardiography
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	Double blinding but unblinding date not stated
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	

reported result	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	LVMI-Wong	**Study ID**	Wong 2012	**Assessor**	Ahmed
Ref or Label	9	**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Metformin	**Comparator**	Placebo	**Source**	
Outcome	LVEF	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	pre-established computer-generated sequence from study drug provider
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Some differences were observed but possibly due to chance
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	N	
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NA	
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	PN	five patients discontinued due to GIT adverse effects
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	36/39 in metformin and 22/23 in placebo
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	

	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	LVMI-Gupta	**Study ID**	Gupta 2020	**Assessor**	Ahmed
Ref or Label		**Aim**	adhering to intervention (the 'per-protocol' effect)	**The effect of adhering to intervention…**	occurance of non-protocol interventions; failures in implementing the intervention that could have affected the outcome; non-adherence to their assigned intervention by trial participants
Experimental	Metformin	**Comparator**	SOC	**Source**	Journal article(s)
Outcome	LVEF	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Random numbers Table and no method of concealment
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PN	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Baseline balanced across groups but some differences were observed in gender, eGFR and HR
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y	No placebo
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	PY	
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PN	
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	NI	All patients probably adhered to meds
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N	
	Risk of bias judgement	**High**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Only 5 patients were excluded
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Echocardiography is objective
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	No pre-defined plan and the study was retrospectively registered on clinical trials.gov
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	

	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	