Supplementary Material

Comparison of troponin and natriuretic peptides in takotsubo syndrome and acute coronary syndrome: a meta-analysis

Liam S Couch[1,2], James Garrard[2], John A Henry[2], Rafail A Kotronias[2], Bashir Alaour[1], Giovanni Luigi De Maria[2], Keith M Channon[2], Adrian P Banning[2], Alexander R Lyon[3], Michael S Marber[1], Thomas E Kaier[1]

[1] King's College London BHF Centre, The Rayne Institute, St Thomas' Hospital, London, UK

[2] Division of Cardiovascular Medicine, Radcliffe Department of Medicine, John Radcliffe Hospital, University of Oxford, Oxford, UK

[3] Department of Cardiology, Royal Brompton Hospital, London, UK

Corresponding author:

Dr Thomas E Kaier, The Rayne Institute, 4th Floor Lambeth Wing, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, UK

Tel: +44-(0)20-7188 1048

Email: thomas.kaier@kcl.ac.uk

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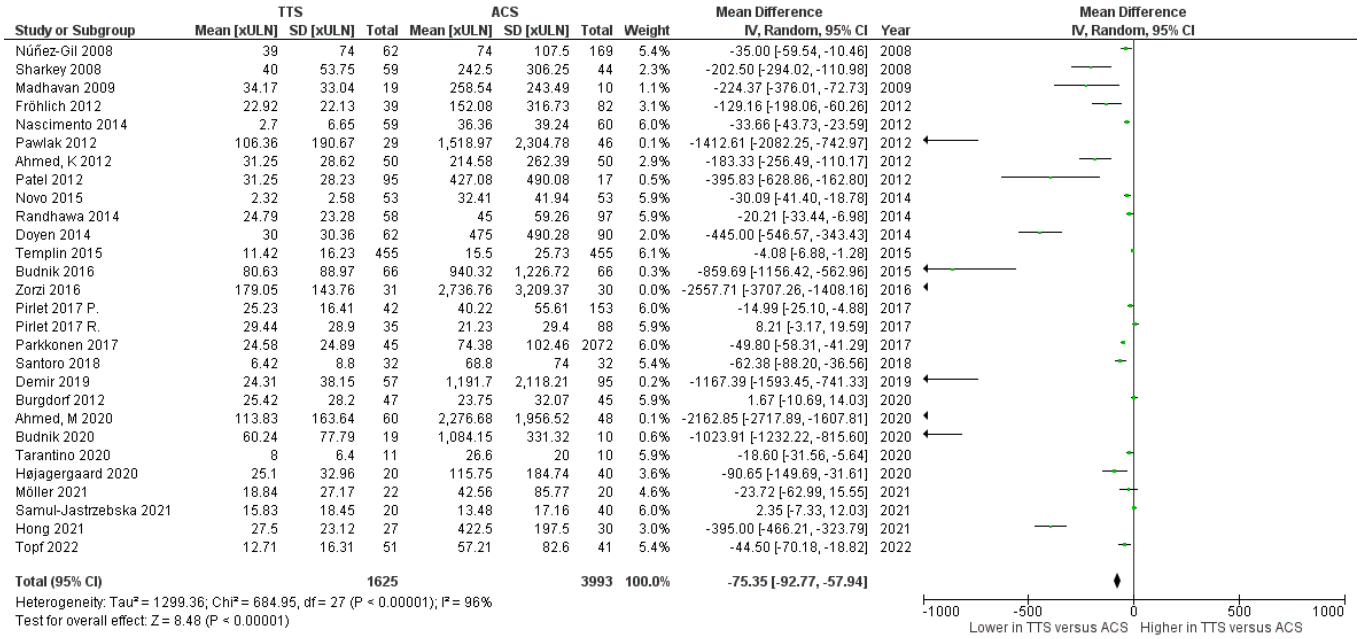

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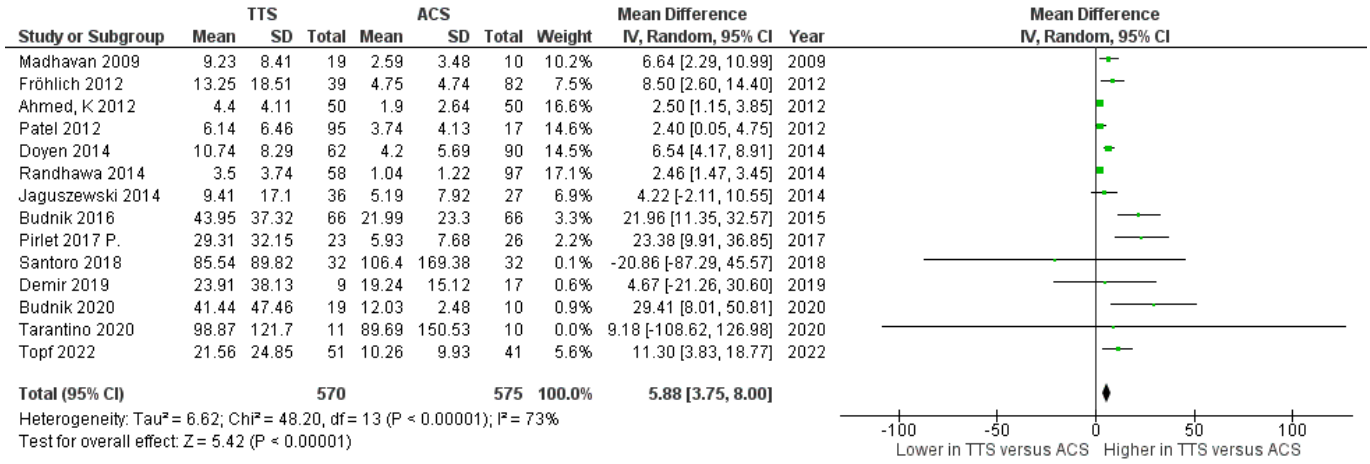

Supplementary Figure 1. Forest plots of the absolute mean difference for troponin in takotsubo syndrome versus acute coronary syndrome

Mean difference shown for included studies in TTS versus ACS for (**A**) troponin and (**B**) NP.

Data displayed as mean +/- SD to 2 decimal places. Studies included within this Forest plot:

[2,6,8,10,19–42]. 'Pirlet 2017 P' and 'Pirlet 2017 R' represent the prospective and retrospective cohorts from this study respectively. TTS = takotsubo syndrome; ACS = acute coronary syndrome; NP = natriuretic peptide.

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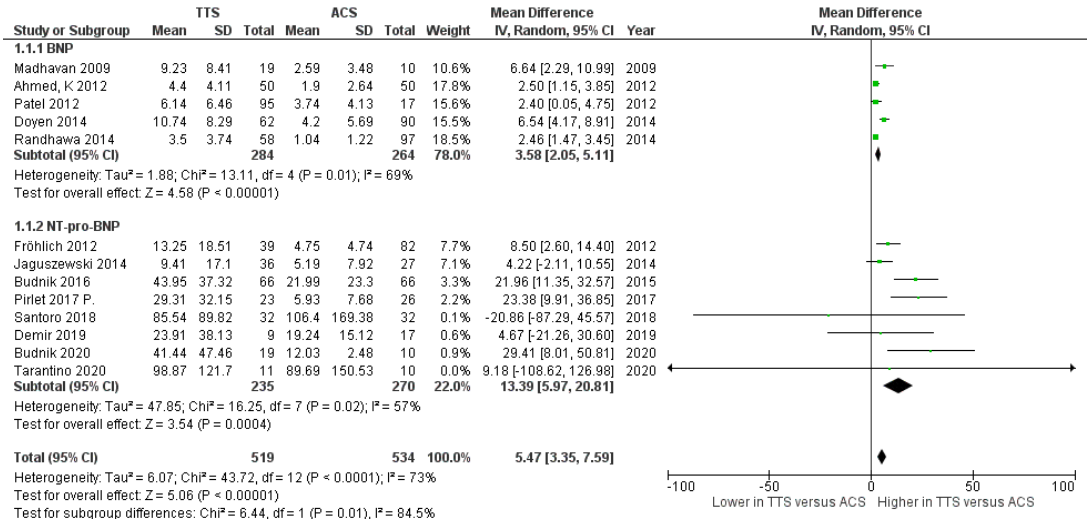

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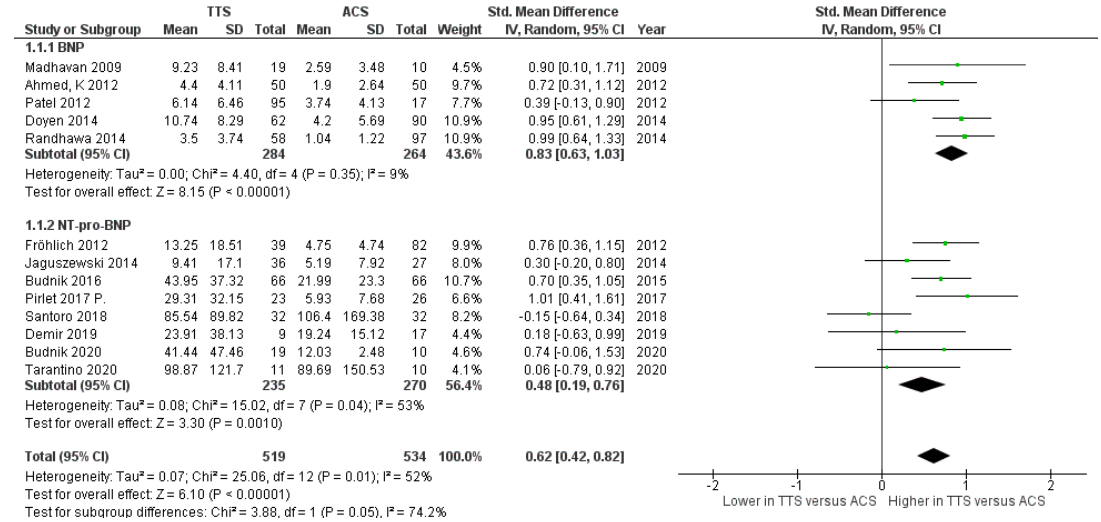
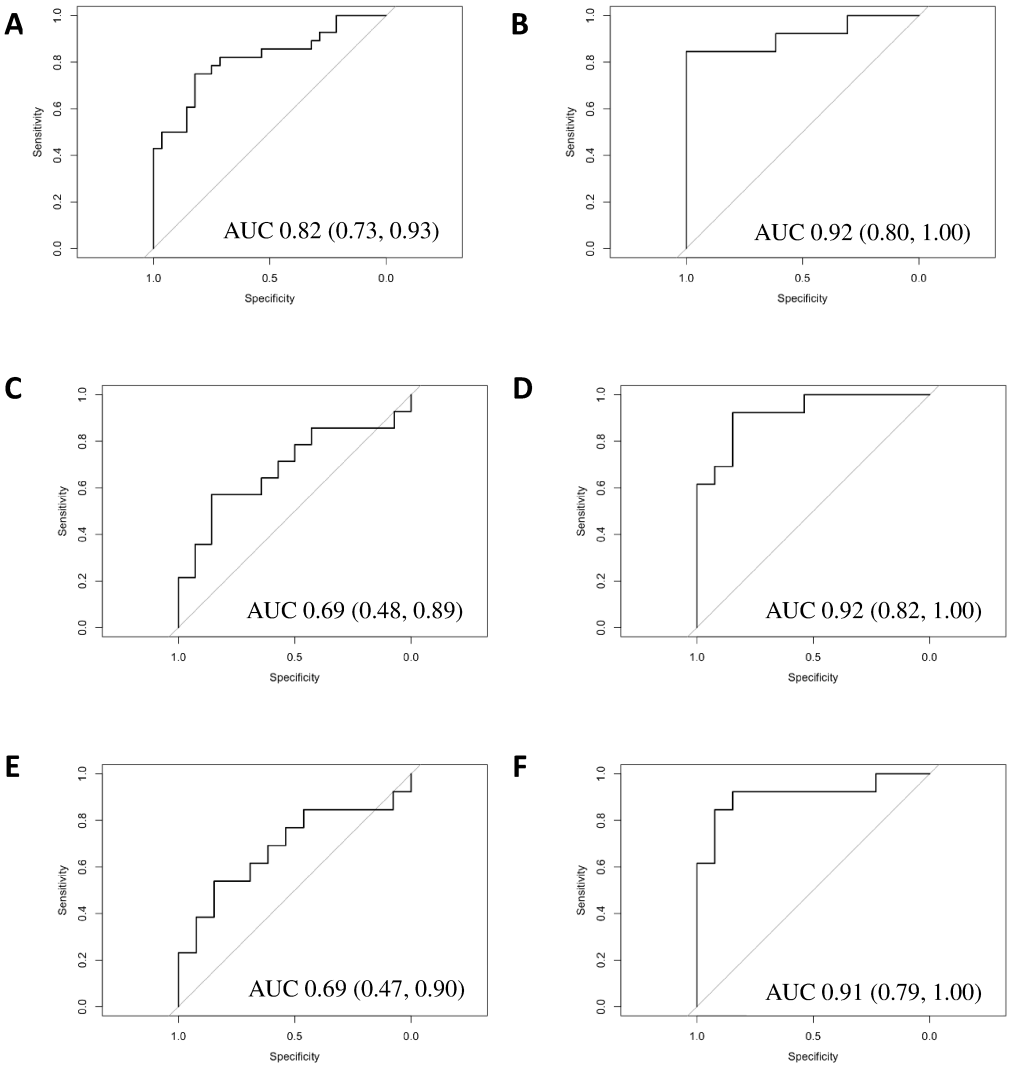


Supplementary Figure 2. Comparison by natriuretic peptide subtype
Standardised mean difference (A) and mean difference (B) shown for TTS versus ACS with studies separated based on natriuretic peptide subtype; BNP or NT-pro-BNP. Data displayed as mean +/- SD to 2 decimal places. Studies included within this Forest plot: [2,6,8,10,19–42]. 'Pirlet 2017 P' and 'Pirlet 2017 R' represent the prospective and retrospective cohorts from this study respectively. TTS = takotsubo syndrome; ACS = acute coronary syndrome; NP = natriuretic peptide.



Supplementary Figure 3. Receiver operating characteristic analysis for troponin and natriuretic peptides

Shown are the ROC curves for troponin in ACS versus TTS (A, N=28 studies), STEMI versus TTS (B, N=13 studies) and for NP in ACS versus TTS (C, N=14 studies). 13 studies were matched for paired analysis of troponin and NP, with troponin for ACS versus TTS (D, N=13 studies) and for NP in ACS versus TTS (E, N=13 studies) shown. Finally, for this paired comparison, NP and troponin combined via logistic regression for ACS versus TTS is shown (F, N=13 studies). ROC curves for sensitivity and specificity shown with AUC (95% CI) shown on each graph respectively. ROC = receiver operating characteristic; ACS = acute coronary syndrome; TTS = takotsubo syndrome; STEMI = ST-segment elevation myocardial infarction; NP = natriuretic peptides.

Supplementary Table 1. Risk of bias analysis using the NHLBI NIH Quality Assessment of Case-Control Studies tool

NHLBI Quality Assessment of Case-Control Studies	Ahmed 2012	Ahmed 2020	Budnik 2016	Budnik 2020	Burgdorf 2012	Demir 2019	Doyen 2014	Fröhlich 2012	Hong 2020	Højagergaard 2020	Jaguszewski 2014	Madhavan 2009	Möller 2021	Nascimento 2014	Novo 2015	Núñez-Gil 2008	Parkkonen 2017	Patel 2012	Pawlak 2012	Pirlet 2017	Randhawa 2014	Samul-Jastrzębska 2021	Santoro 2018	Sharkey 2008	Tarantino 2020	Templin 2015	Topf 2022	Zorzi 2016
Was the research question or objective in this paper clearly stated and appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the authors include a sample size justification?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	Yes	Yes	Yes	NR	Yes	No	Yes	Yes	NR	Yes	CD	CD	Yes	Yes	NR	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the cases clearly defined and differentiated from controls?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	NR	No	No	No	No	No	No	NR	NR	No	No	No	NA	No	No	NA	NA	No	NA	Yes	No	No	No	No	No	NR	No	No
Was there use of concurrent controls?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	NA	No	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CD	NA	No	No	NA	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	NR	Yes
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the assessors of exposure/risk blinded to the case or control status of participants?	NR	Yes	No	Yes	Yes	NR	No	NR	No	NR	NR	No	NR	NR	NR	NR	NR	Yes	NR	NR	NR	NR	NR	NR	Yes	NR	NR	Yes
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	Yes	No	No	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Quality Rating (Good/Fair/Poor)	Fair	Poor	Fair	Poor	Good	Fair	Good	Good	Fair	Good	Fair	Fair	Good	Fair	Fair	Fair	Good	Fair	Good	Good	Good	Fair	Good	Good	Good	Fair	Fair	Good

Corresponding studies were evaluated for presence of bias by answering questions shown. NHLBI = National Heart, Lung and Blood Institute; NIH = National Institute of Health; CD = cannot determine; NA = not applicable; NR = not reported.

Supplementary Table 2. Sensitivity and heterogeneity analysis for troponin and natriuretic peptides for standardised mean difference of included studies

Sensitivity analysis domain	Troponin			NP		
	Number of studies / participants	SMD (95% CI)	Heterogeneity (I^2)	Number of studies / participants	SMD (95% CI)	Heterogeneity (I^2)
All studies	28 / 5,618	-0.86 (-1.08, -0.64)	89%	14 / 1,145	0.62 (0.44, 0.80)	49%
Study design: excludes retrospective studies	15 / 1,383	-0.87 (-1.18, -0.56)	84%	8 / 557	0.62 (0.32, 0.92)	59%
Sex: excludes female only studies	21 / 4,998	-0.66 (-0.88, -0.45)	86%	10 / 772	0.60 (0.34, 0.86)	63%
Sex: female only studies	7 / 620	-1.49 (-1.99, -0.99)	85%	4 / 373	0.65 (0.42, 0.88)	0%
Sex: excludes studies with unequal sex distribution	21 / 2,773	-0.89 (-1.16, -0.62)	89%	13 / 990	0.58 (0.39, 0.77)	44%
Biomarker: excludes studies where time of biomarkers not specified	20 / 1,816	-0.82 (-1.09, -0.55)	85%	11 / 938	0.59 (0.39, 0.80)	52%
Risk of bias: excludes studies with high risk of bias	26 / 5,481	-0.76 (-0.97, -0.56)	87%	13 / 1,116	0.61 (0.42, 0.81)	52%

NP = natriuretic peptide; SMD = standardised mean difference; CI = confidence interval.

Supplementary Table 3. Sensitivity and heterogeneity analysis for troponin and natriuretic peptides for mean difference of included studies

Sensitivity analysis domain	Troponin			NP		
	Number of studies / participants	Mean difference (95% CI)	Heterogeneity (I^2)	Number of studies / participants	Mean difference (95% CI)	Heterogeneity (I^2)
All studies	28 / 5,618	-75.35 (-92.77, -57.94)	96%	14 / 1,145	5.88 (3.75, 8.00)	73%
Study design: excludes retrospective studies	15 / 1,383	-86.11 (-115.30, -56.92)	95%	8 / 557	9.09 (5.58, 12.59)	41%
Sex: excludes female only studies	21 / 4,998	-51.07 (-65.77, -36.37)	95%	10 / 772	6.65 (3.65, 9.66)	68%
Sex: female only studies	7 / 620	-1087.48 (-1548.48, -626.48)	95%	4 / 373	6.45 (1.59, 11.31)	84%
Sex: excludes studies with unequal sex distribution	21 / 2,773	-99.48 (-124.74, -74.21)	95%	13 / 990	7.23 (4.41, 10.05)	72%
Biomarker: excludes studies where time of biomarkers not specified	20 / 1,816	-58.77 (-78.03, -39.51)	94%	11 / 938	5.30 (3.12, 7.48)	71%
Risk of bias: excludes studies with high risk of bias	26 / 5,481	-61.89 (-77.61, -46.17)	95%	13 / 1,116	5.52 (3.49, 7.55)	72%

NP = natriuretic peptide; SMD = standardised mean difference; CI = confidence interval.