

Francisco Miguel Marujo Pinheiro
O papel da Biópsia Líquida e do
DNA celular livre na doença
cardiovascular – Uma Revisão
Sistemática/ The role of Liquid
Biopsy and cell-free DNA in
cardiovascular pathology - A Systematic Review

Maio 2022

Francisco Miguel Marujo Pinheiro

O papel da Biópsia Líquida e do DNA
celular livre na doença cardiovascular –
Uma Revisão Sistemática/ The role of
Liquid Biopsy and cell-free DNA in
cardiovascular pathology- A systematic
review

Mestrado Integrado em Medicina

Área: Patologia Clínica

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:
Professora Doutora Sandra Paula da Costa Pinto da Silva
Rebelo

Trabalho organizado de acordo com as normas da revista:
American Heart Journal

Junho 2022

Eu, Francisco Miguel Marujo Pinheiro, abaixo assinado, nº mecanográfico 201607395, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 23/03/2022

Assinatura conforme cartão de identificação:

Assinado por: **Francisco Miguel Marujo Pinheiro**
Num. de Identificação: 13950287
Data: 2022.03.24 23:23:32+00'00'



NOME

Francisco Miguel Marujo Pinheiro

NÚMERO DE ESTUDANTE

201607395

E-MAIL

fpinheiro921@gmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

Medicina Clínica – Patologia Clínica

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

O papel da Biópsia Líquida e do DNA celular livre na doença cardiovascular – Uma Revisão Sistemática/ The role of Liquid Biopsy and cell-free DNA in cardiovascular pathology - A Systematic Review

ORIENTADOR

Professora Doutora Sandra Paula da Costa Pinto da Silva Rebelo

COORIENTADOR (se aplicável)

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTES TRABALHOS APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTES TRABALHOS (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTES TRABALHOS.	☒

Faculdade de Medicina da Universidade do Porto, 23/03/2022

Assinatura conforme cartão de identificação:

Assinado por: **Francisco Miguel Marujo Pinheiro**
Num. de Identificação: 13950287
Data: 2022.03.24 23:24:03+00'00'

Abstract

Background: As Medicine evolves, so do diagnostic procedures, therapies and disease monitoring tools. One of the areas that is under great development is precision medicine. Finding a way to adapt treatments, not only to disease, but also to specific patients is, undoubtedly, a way to make treatments much more successful. Within this topic, liquid biopsy has risen to a state of a very promising technology in the field of oncology. It has shown great potential for diagnostics and monitoring by detecting rising levels of tumor-DNA in the blood way before the disease has imaging proof of progression. Consequently, the hypothesis of applying this technology to other fields is quite legitimate. Alternative and less invasive indicators of cardiovascular disease are important and liquid biopsy can be a powerful option. By analyzing the circulating DNA in the blood, it is possible to investigate specific molecular changes in each patient and use that information to better adjust therapy, evaluate prognostic and risk or even detect early signs of transplant rejection.

Material & Methods: This review aimed at systematically investigate if liquid biopsy can be a useful tool to improve medical practice in the clinical setting of myocardial infarction (MI), heart failure (HF) and heart transplantation (HTx). PubMed and Web of Science were searched for studies that reported cfDNA levels in the blood, plasma or urine of adults and/or children and related those levels with MI, HF or HTx. Studies in other language apart from English were excluded, as well as other reviews.

Results: From 186 search results, 15 studies were included. The studies reported higher levels of cell-free DNA (cfDNA) in the blood and/or plasma of patients who suffered a myocardial infarction, who had heart failure of an ischemic nature and who registered higher rates of heart transplant rejection.

Conclusions: According to the information reported by the included studies, liquid biopsy seems to have several different applications in the field of cardiology. Not only it has shown positive correlation with existing cardiac biomarkers, but also has been proven to be very sensible to therapy adjustments and disease progression. However, further investigation is still warranted since there is a lack of a standard collection and quantification method, as well as larger sample size studies.

Key words: liquid biopsy, cell-free DNA, myocardial infarction, heart failure, heart transplant

Introduction

Rationale

Cell-free DNA (cfDNA) is fragmented DNA that circulates through the body in several different fluids, such as blood, plasma and cerebrospinal fluid. Its levels rise under certain conditions like exercise, increased age and in certain pathological situations. cfDNA has shown to be promising in Oncology [1-3], and, based on that premise, the demand for investigation for other possible uses has increased. One field that is exploring new uses for cfDNA is cardiovascular diseases (CVD). According to the literature, conditions such as myocardial infarction (MI) and heart failure (HF) can alter the circulating levels of cfDNA. [4-7] Moreover, cfDNA has also been studied as a tool for evaluating possible organ rejection after a heart transplant. [8-12] Despite the multiples studies regarding cfDNA, several aspects concerning, for instance, the sources that release cfDNA into the bloodstream, need to be better understood. It is thought that cfDNA can result from cellular breakdown due to necrosis/apoptosis or it can be active released as a result of normal cellular metabolism.

Objectives

This systematic review aims at enlightening the possible application of cfDNA in cardiac pathology. Since the field of cardiology is rather vast, this work will explore the benefits that cfDNA can add regarding diagnosis, treatment and prognosis of adults with MI, HF and heart transplant (HTx).

In the setting of a MI, cfDNA levels are being compared to the levels of other cardiac biomarkers such as: troponin and creatine kinase, showing promising results and strong correlation. Additionally, it can also be used as a follow-up tool after percutaneous coronary intervention. [13, 14]

Regarding HF, cfDNA apparently has potential to better characterize the disease, mainly as a tool to determine the amount of cellular damage present and evaluating myocardial performance. [6, 7]

Finally, the *gold standard* to evaluate rejection after a HTx is an endomyocardial biopsy, which is an invasive procedure. If cfDNA could be used as a non-invasive way to acquire the same information, not only it would be beneficial for the patient because it is less invasive, but also more cost-effective. [4-7, 15, 16]

Methods

Inclusion and exclusion criteria

All studies that reported cfDNA levels in the plasma or urine of adults and related those levels with MI, HF or HTx were eligible for inclusion. Moreover, all study designs were also qualified for inclusion. We excluded studies in any language other than English and where no translation was available. Additionally, reviews were also excluded. Duplicate studies were also excluded.

Search strategy

A systematic search of the literature regarding the role of cfDNA in MI, HF and HTx was implemented by the researchers. The databases PubMed and Web of Science were used, and the chosen MESH search terms were “cell free DNA, cfDNA”, “liquid biopsy”, “myocardial infarction”, “heart transplant” and “heart failure”. Several different spellings were also tested, as well as different abbreviations, in order to account for the heterogeneity of the research field. The abstracts were reviewed by two researchers (S.R. and F.P.).

Risk of Bias

The risk of bias assessment was made by two independent authors, using the National Institute of Health Criteria [17].

Results of this analysis are present in the appendix, *Table 1 and 2*.

Results

Myocardial Infarction

According to Zemmour, *et al.*, cfDNA has a dramatical increase in patients who suffered a ST- elevation myocardial infarction (STEMI). Moreover, in their study, which included 57 patients, cfDNA values show high correlation when compared to troponin levels (Spearman correlation of 0.79 and p -value < 0,0001). [13]

This correlation was also reported by Shimony, *et al.*. In their study, they measured cfDNA, troponin and creatine kinase (CK) concentrations of 16 randomly selected patients with an acute STEMI upon admission. Not only cfDNA values were higher than

the control samples ($p < 0,001$), but also correlated to CK (Pearson's r-test value of $R = 0,79$; $p < 0,001$) and troponin ($R = 0,65$; $p = 0,006$) values. [14]

Similar findings were also reported by Cui, *et al.*. In a study of cfDNA plasma concentrations of 137 patients with acute coronary syndrome (ACS), 60 controls and 13 patients with stable angina (SA). Higher levels of cfDNA were found in ACS (median of 2285 ng/mL, $p < 0.05$) patients than in SA (median of 202.3 ng/mL, $p < 0.05$) and healthy patients (median of 118.3 ng/mL, $p < 0.05$). Moreover, when evaluating the cfDNA within the ACS group, they observed higher cfDNA levels in STEMI patients than in non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina (UA) (median 5745 ng/mL vs median 2725 ng/mL and 802 ng/mL, respectively). Moreover, they registered a positive correlation between cfDNA, CK and troponin, with $R = 0.669$ and $R = 0.724$, respectively. [18]

Antonatos *et al.*, studied 13 patients admitted with acute myocardial infarction who went thrombolysis within 6 hours from the onset of chest pain. Their study also reported statistically significant higher cfDNA levels in patients than controls (6873 g.e./mL vs. 4112 g.e./mL, $P < 0.0001$) and in patients with complications vs. patients without complications (1298 g.e./mL vs 245 g.e./mL). Additionally, they also report maximum correlation of CK and troponin with cfDNA levels (R values of 0,62 and 0,68, respectively, for the first day postinfarction and 0,57 and 0,72, respectively, for the second day postinfarction). [19]

Heart Failure

The application of cfDNA in the clinical setting of heart failure is still in its beginning. According to the data search and chosen criteria, only one study was included. Yokokawa *et al.*, studied 32 patients with HF and 28 healthy controls and showed that cardiomyocyte-specific cfDNA (which was identified through PCR and a specific methylation pattern at locus FAM101A), was significantly elevated in heart failure patients when compared with the controls (median 0.99 [IQR, 0.77-1.98] vs 0 [0-0.91] copies/mL, $P = 0.003$). Moreover, they measured a positive correlation with troponin I and no correlation with B-type natriuretic peptide (BNP). [15]

Heart Transplant

Zangwill, *et al.*, described the behavior of the donor fraction (DF) cfDNA, which peak two days after the transplant, suffering a decline towards the baseline in the following 6 to 9

days. However, in patients with worse prognosis, there was a lagged decline of DF cfDNA towards the baseline or the total cfDNA levels were higher in the first week after transplantation (41,5 ng/mL, in patients who died, vs 13,6 ng/mL in patients who survived, $p = 0.07$). More specifically, they reported 4 deaths: 3 with both conditions and 1 with blunted DF cfDNA decline. [20]

Likewise, Macher *et al.* reported similar results. During their study, 30 patients were evaluated post-heart transplant. They registered 4 deaths, none of which due to heart rejection. Severe rejection was described in 3 of the 30 patients but it was controlled after immunosuppressants adjustment. In the end, they reported a cfDNA spike preceding a rejection diagnosis by biopsy, as well as increased cfDNA levels when there was graft injury due to heart damage. Additionally, they also verified that cfDNA peaks 24 hours after transplant and drops to baseline levels 3 to 4 days post-transplant. In patients with complications, they registered a significantly lagged decay, just like the previous studies mentioned. [21]

Since endomyocardial biopsy (EMB) is the gold standard for confirming rejection, and it is an invasive procedure, gene expression profiling (GEP) is being used as a way to evaluate the need for performing an EMB. Gondi, *et al.*, investigated the use of donor derived cfDNA (ddcfDNA) in combination with GEP as a tool for reclassifying risk patients and compared it with the GEP-only protocol. Due to cfDNA's high negative predictive value, it was possible to reduce the number of EMB in 12.7% when compared to the GEP-only assessment. These results were from evaluations in the timeframe of 6 or more months post-transplant. [22]

Regarding the need for a safer alternative for EMB, Bienkowski *et al.* studied 21 EMB and blood samples of 9 patients, which were taken post-transplant. Four samples were graded 0R and seventeen 1R in terms of an acute cellular rejection scale. Only two of those classified as 1R showed increased ddcfDNA. One matched with an ambiguous histology with dense lymphocytic infiltration but still no signs of rejection, while the other was taken from a patient suffered from cardiac tamponade and cardiac arrest. Although the results are not conclusive, since there was no histological evidence of clear rejection, ddcfDNA was very sensible to clinical complications, such as cardiac tamponade and cardiac arrest, which resulted in a very expressive rise in its levels. [23]

Also, concerning the topic of rejection diagnosis, Khush *et al.*, collected venous blood from 740 HTx patients from 26 centers and in a single-center cohort of 33 patients at high risk for antibody-mediated rejection (AMR). In their study, cfDNA levels registered a median of 0.07% for reference HTx patients (2164 samples) and 0.17% for patients in

acute rejection (35 samples, $p = 0.005$). Furthermore, Khush *et al*, also evaluated cfDNA levels for specific types of rejection, more specifically, AMR and acute cellular rejection (ACR). Both types of rejection achieved higher levels of cfDNA when compared to patients without rejection (0.17% and 0.12% vs 0.07%, respectively; $p = 0.104$). Furthermore, when also taking into consideration the severity of rejection for the different types, they found even higher levels: AMR and ACR cfDNA median levels were 0.74% and 0.25% (for ACR grade $\geq 2R$, and AMR grade $\geq pAMR1$) vs 0.09% for non-rejection cases. In the end, and setting the cfDNA threshold of 0.2%, evaluating rejection through this method has a 44% sensitivity and an 97% negative predictive value. [24]

Additionally, Richmond *et al*, evaluated 241 heart transplant patients from 7 centers, with transplant ages ranging from 8 days to 73 years old. DF cfDNA was quantified and performed well in distinguishing allograft problems in AMR and ACR. The AMR was evaluated using a whole-blood protocol and it showed a robust association between higher levels of DF fraction and higher grades of AMR rejection. However, due to possible dilution of DF fraction accounted by cell lysis, a plasma-only analysis needed to be performed to better evaluate the ACR case. Nonetheless, DF as a rejection screening tool was shown to be promising. In the study, DF in ACR 1R/2R ($n = 15$) was higher than ACR 0R ($n = 42$) ($p = 0.02$) and DF in antibody-mediated rejection severity of pAMR1 ($n = 8$) and pAMR2 ($n = 12$) was higher than for pAMR0 ($n = 466$) ($p = 0.05$ respectively). [25]

Discussion

Besides its usefulness in oncology, cfDNA poses as a promising organ specific biomarker within the field of cardiology. Although it is still a new technology, and further testing is needed, it has provided robust results in terms of diagnosis, risk stratification and prognosis evaluation of cardiovascular diseases. Moreover, cfDNA can also be applied to evaluate the extent of cardiomyocyte death in heart failure [15] and has shown high negative predictive value when evaluating the presence of acute cellular rejection and antibody mediated rejection in heart transplants [24, 25], which makes it interesting as an alternative for the endomyocardial biopsy, the gold standard method used for monitoring rejection of heart transplants [22].

Myocardial Infarction

cfDNA can be a useful biomarker for MI. Compared to healthy controls, MI patients can have their cfDNA levels increase more than 25-fold before treatment and, usually, within 2 hours of the onset of chest pain (with a AUC of 0.94, indicating high sensitivity and specificity). [13] In contrast, troponin can be detected as early as 6 hours post-MI [26]. Following therapy, cfDNA levels return to baseline in about 1 to 2 days while troponin clearance can take as much as 14 days. [13, 26]

Due to these rapid clinical responses, cfDNA may serve as a powerful test to evaluate the onset of a MI (as a component of a multimarker diagnostic panel), as well as a tool for monitoring immediate treatment response, which is also supported by Xie, *et al.* [27].

Several other studies also support the idea of adding cfDNA in a MI multimarker diagnostic panel. Shimony *et al.*, Cui *et al.*, and Antonatos *et al.*, found evidence of a positive correlation between cfDNA, troponin and CK peak levels. [14, 18, 19]

Furthermore, there are other several scenarios, like post-exercise myocardial strain and secondary myocardial injury due to acute illness, that can cause a rise in troponin levels. However, these cases represent reversible myocardial injury and not actual cell necrosis. [28, 29] If studies formally demonstrate a clear proof that cfDNA is exclusively released in the case of cell death and not in reversible myocardial injury, it can help in distinguishing cardiomyocyte death from reversible damage [13].

In addition, it has been clearly established that chronic kidney disease can cause a rise in troponin levels [30]. By using cardiomyocyte-specific cfDNA, which is cleared by the liver and not affected by changes in kidney function, we can better evaluate the presence of cardiomyocyte death in a patient with concomitant renal disease [13].

Other use of cfDNA regards the risk stratification for acute coronary syndromes (ACS). According to Cui *et al.*, STEMI patients have higher cfDNA concentrations compared to UA and NSTEMI patients. This fact was thought to be related to the physiopathological process behind the development of a STEMI, in which there is progressive necrosis of the heart muscle. Taking into consideration the hypothesis that cfDNA is released in the event of cell death, it is logical to assume that conditions in which there is a higher degree of necrosis will result in higher levels of cfDNA in the blood. Additionally, Cui *et al.* also studied the relation between cfDNA levels and the GRACE and Gensini scoring systems for patients with ACS, which showed an increase in cfDNA levels with higher risk scores. [18]

Collectively, these studies seem to indicate that a strong relation between cfDNA quantities released into the bloodstream and the severity/extent of the myocardial lesion may exist.

Heart Failure

Yokokawa *et al.*, using their protocol based on PCR and specific DNA methylation patterns, were able to identify increased cardio-specific cfDNA in heart failure patients, being the first study to do so. Moreover, they also found no significant correlation between cfDNA and BNP, which suggests that cfDNA will probably not be very useful in monitoring the disease since symptoms and progression are closely related to the BNP levels. However, since it is thought that cfDNA is released in cell death, high levels of cardio-specific cfDNA in patients with heart failure may be useful to evaluate if the cardiomyopathy in question is of an ischemic nature. Finally, Yokokawa *et al.* results also seem to support other previous findings, more specifically, the correlation with troponin levels, as well as it not being affected by kidney function. [15]

Heart Transplant

In heart transplant patients, rejection is usually monitored through endomyocardial biopsy, which is the gold standard technique. However, this is an invasive procedure with several possible complications, such as: cardiac perforation with tamponade, supraventricular tachycardia or atrioventricular conduction abnormalities [31]. Taking that into consideration, developing a less invasive way of predicting rejection is of interest.

Although there is not a standardized protocol of collection, analysis and reporting of cfDNA, which can explain the different sensibility and specificity across the studies, the majority described a higher negative predictive value (Table 1). These results suggest that cfDNA analysis is more appropriate for the exclusion of transplant rejection in this context.

Furthermore, studies reported a rise in cfDNA levels up to three-months before biopsy-proven rejection in patients with long term therapy and when there is graft injury due to heart damage. These findings bring to discussion the use of cfDNA to predict rejection, as well as a follow-up tool for immunotherapy dose adjustments and compliance evaluation. [20, 21] Moreover, a study by Richmond *et al.* reported better performance of cfDN for detecting higher grades of rejection, achieving an NPV (negative predictive value) of 80% for grades ≥ 1 in antibody mediated rejection and 1R in acute cellular rejection. Additionally, this study also showed the same performance in pediatric cardiology (NPV of 81,8%), which is an area lacking investigation regarding this topic [25].

Last but not least, other data supports the use of cfDNA for monitoring heart transplant rejection in a study performed by Hollander, *et al.*, where they estimated that a blood-based biomarker compared with endomyocardial biopsy for the diagnosis of acute allograft rejection may result in a cost saving of \$27,244 and QALY gain of 0,046 on average during the first 5 years post-transplant. [32]

Studies Limitations

The main problem reported by several studies was the fact that number of patients evaluated was not large enough to be able to perform a more detailed and significant analysis. Besides, some studies used only patients from a single clinical center, which can also introduce a selection bias into the results. [14, 15, 18-21, 25]

Furthermore, there is still a lack of standardization and consistency concerning sample collection and processing methods of cfDNA. [20, 22, 23, 33-35]

Advantages and Disadvantages of cfDNA

Taking into consideration the information gathered from the selected studies, it appears that cfDNA can be a promising tool in the field of cardiology. Not only as a diagnostic

test, but also as a prognostic tool and a way to monitor therapeutic responses. Its advantages include:

- Initial levels of cfDNA can correlate with levels of organ injury and possible long term function
- Can help tailor immunosuppression
- Can function as liquid biopsy and possibly replace EMB
- Can be used across all solid organ transplantations
- Easier to standardize and remove interpretation bias
- More cost-effective

[10, 32]

However, several disadvantages have been identified, mainly in terms of standardization regarding the samples collection and processing. While some studies analyzed the amounts of cfDNA through PCR, others used spectrophotometry techniques. Moreover, even within the type of PCR techniques, there was also variation. Some studies used real-time PCR while others used digital droplet PCR, which also influenced the period of time between sample collection and results release. Furthermore, and even though the number of studies is increasing, endomyocardial biopsy is still the gold standard and more studies are needed to confirm cfDNA utility, not only in adult but also in pediatric cardiology. [10]

Limitations of the review

Since this study is a summary of several different manuscripts on the subject, in the absence of a meta-analysis it can only provide a qualitative analysis of the utility of cfDNA within the different clinical settings explored.

Conflict of Interest

The author certifies that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding

No funding received for this review.

Bibliography

1. Jiang, T., et al., *The diagnostic value of circulating cell free DNA quantification in non-small cell lung cancer: A systematic review with meta-analysis*. Lung Cancer, 2016. **100**: p. 63-70.
2. Aucamp, J., et al., *The diverse origins of circulating cell-free DNA in the human body: a critical re-evaluation of the literature*. Biol Rev Camb Philos Soc, 2018. **93**(3): p. 1649-1683.
3. Bodelon, C., et al., *Blood DNA methylation and breast cancer risk: a meta-analysis of four prospective cohort studies*. Breast Cancer Res, 2019. **21**(1): p. 62.
4. Polina, I.A., D.V. Ilatovskaya, and K.Y. DeLeon-Pennell, *Cell free DNA as a diagnostic and prognostic marker for cardiovascular diseases*. Clinica Chimica Acta, 2020. **503**: p. 145-150.
5. Bayes-Genis, A. and D. Lanfear, *Liquid Biopsy and eHealth in Heart Failure The Future Is Now*. Journal of the American College of Cardiology, 2019. **73**(17): p. 2206-2208.
6. Benincasa, G., G. Mansueto, and C. Napoli, *Fluid-based assays and precision medicine of cardiovascular diseases: the 'hope' for Pandora's box?* Journal of Clinical Pathology, 2019. **72**(12): p. 785-799.
7. Mansueto, G., et al., *Epigenetic-sensitive liquid biomarkers and personalised therapy in advanced heart failure: a focus on cell-free DNA and microRNAs*. Journal of Clinical Pathology, 2020. **73**(9): p. 535-543.
8. Kittleson, M.M. and S. Garg, *Solid Gold, or Liquid Gold? Towards a New Diagnostic Standard for Heart Transplant Rejection*. Circulation, 2021. **143**(12): p. 1198-1201.
9. Knight, S.R., A. Thorne, and M.L. Lo Faro, *Donor-specific Cell-free DNA as a Biomarker in Solid Organ Transplantation. A Systematic Review*. Transplantation, 2019. **103**(2): p. 273-283.
10. Sharma, D., et al., *Cell-free DNA in the surveillance of heart transplant rejection*. Indian Journal of Thoracic and Cardiovascular Surgery, 2021. **37**(3): p. 257-264.
11. Beck, J., et al., *Digital Droplet PCR for Rapid Quantification of Donor DNA in the Circulation of Transplant Recipients as a Potential Universal Biomarker of Graft Injury*. Clinical Chemistry, 2013. **59**(12): p. 1732-1741.
12. Oellerich, M., et al., *Graft-Derived Cell-Free DNA as a Marker of Transplant Graft Injury*. Therapeutic Drug Monitoring, 2016. **38**: p. S75-S79.
13. Zemmour, H., et al., *Non-invasive detection of human cardiomyocyte death using methylation patterns of circulating DNA*. Nature Communications, 2018. **9**.
14. Shimony, A., et al., *Cell free DNA detected by a novel method in acute ST-elevation myocardial infarction patients*. Acute Card Care, 2010. **12**(3): p. 109-11.
15. Yokokawa, T., et al., *Clinical Significance of Circulating Cardiomyocyte-Specific Cell-Free DNA in Patients With Heart Failure: A Proof-of-Concept Study*. Can J Cardiol, 2020. **36**(6): p. 931-935.
16. Salzano, A., et al., *Circulating cell-free DNA levels are associated with adverse outcomes in heart failure: testing liquid biopsy in heart failure*. European Journal of Preventive Cardiology.
17. Higgins, J. and D. Altman, *Assessing Risk of Bias in Included Studies*. 2008: p. 187-241.
18. Cui, M., et al., *Cell-Free circulating DNA: a new biomarker for the acute coronary syndrome*. Cardiology, 2013. **124**(2): p. 76-84.
19. Antonatos, D., et al., *Cell-free DNA levels as a prognostic marker in acute myocardial infarction*. Ann N Y Acad Sci, 2006. **1075**: p. 278-81.
20. Zangwill, S.D., et al., *Early changes in cell-free DNA levels in newly transplanted heart transplant patients*. Pediatr Transplant, 2020. **24**(1): p. e13622.

21. Macher, H.C., et al., *Donor-specific circulating cell free DNA as a noninvasive biomarker of graft injury in heart transplantation*. Clinica Chimica Acta, 2019. **495**: p. 590-597.
22. Gondi, K.T., et al., *Single-center utilization of donor-derived cell-free DNA testing in the management of heart transplant patients*. Clinical Transplantation, 2021. **35**(5).
23. Bienkowski, M., et al., *Liquid biopsy for minimally invasive heart transplant monitoring: a pilot study*. Journal of Clinical Pathology, 2020. **73**(8): p. 507-510.
24. Khush, K.K., et al., *Noninvasive detection of graft injury after heart transplant using donor-derived cell-free DNA: A prospective multicenter study*. American Journal of Transplantation, 2019. **19**(10): p. 2889-2899.
25. Richmond, M.E., et al., *Donor fraction cell -free DNA and rejection in adult and pediatric heart transplantation*. Journal of Heart and Lung Transplantation, 2020. **39**(5): p. 454-463.
26. Daubert, M.A. and A. Jeremias, *The utility of troponin measurement to detect myocardial infarction: review of the current findings*. Vasc Health Risk Manag, 2010. **6**: p. 691-9.
27. Xie, J., J. Yang, and P. Hu, *Correlations of Circulating Cell-Free DNA With Clinical Manifestations in Acute Myocardial Infarction*. Am J Med Sci, 2018. **356**(2): p. 121-129.
28. Hochstadt, A., Y. Meroz, and G. Landesberg, *Myocardial dysfunction in severe sepsis and septic shock: more questions than answers?* J Cardiothorac Vasc Anesth, 2011. **25**(3): p. 526-35.
29. Shave, R., et al., *Exercise-induced cardiac troponin elevation: evidence, mechanisms, and implications*. J Am Coll Cardiol, 2010. **56**(3): p. 169-76.
30. Michos, E.D., et al., *AHRQ Comparative Effectiveness Reviews, in Cardiac Troponins Used as Diagnostic and Prognostic Tests in Patients With Kidney Disease*. 2014, Agency for Healthcare Research and Quality (US): Rockville (MD).
31. Saraiva, F., et al., *Complications of endomyocardial biopsy in heart transplant patients: a retrospective study of 2117 consecutive procedures*. Transplant Proc, 2011. **43**(5): p. 1908-12.
32. Hollander, Z., et al., *Cost-Effectiveness of a Blood-Based Biomarker Compared to Endomyocardial Biopsy for the Diagnosis of Acute Allograft Rejection*. The Journal of Heart and Lung Transplantation, 2016. **35**(4): p. S53.
33. Agbor-Enoh, S., et al., *Applying rigor and reproducibility standards to assay donor-derived cell-free DNA as a non-invasive method for detection of acute rejection and graft injury after heart transplantation*. J Heart Lung Transplant, 2017. **36**(9): p. 1004-1012.
34. Li, J., B. Richmond, and T.T. Hong, *Cardiac T-Tubule cBIN1-Microdomain, a Diagnostic Marker and Therapeutic Target of Heart Failure*. International Journal of Molecular Sciences, 2021. **22**(5).
35. Catez, E., et al., *Atypical presentation of tuberculous constrictive pericarditis: case report and review of the literature*. Acta Cardiologica, 2012. **67**(3): p. 337-342.

Appendix

Figure 1 - Results of the systematic search - From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1

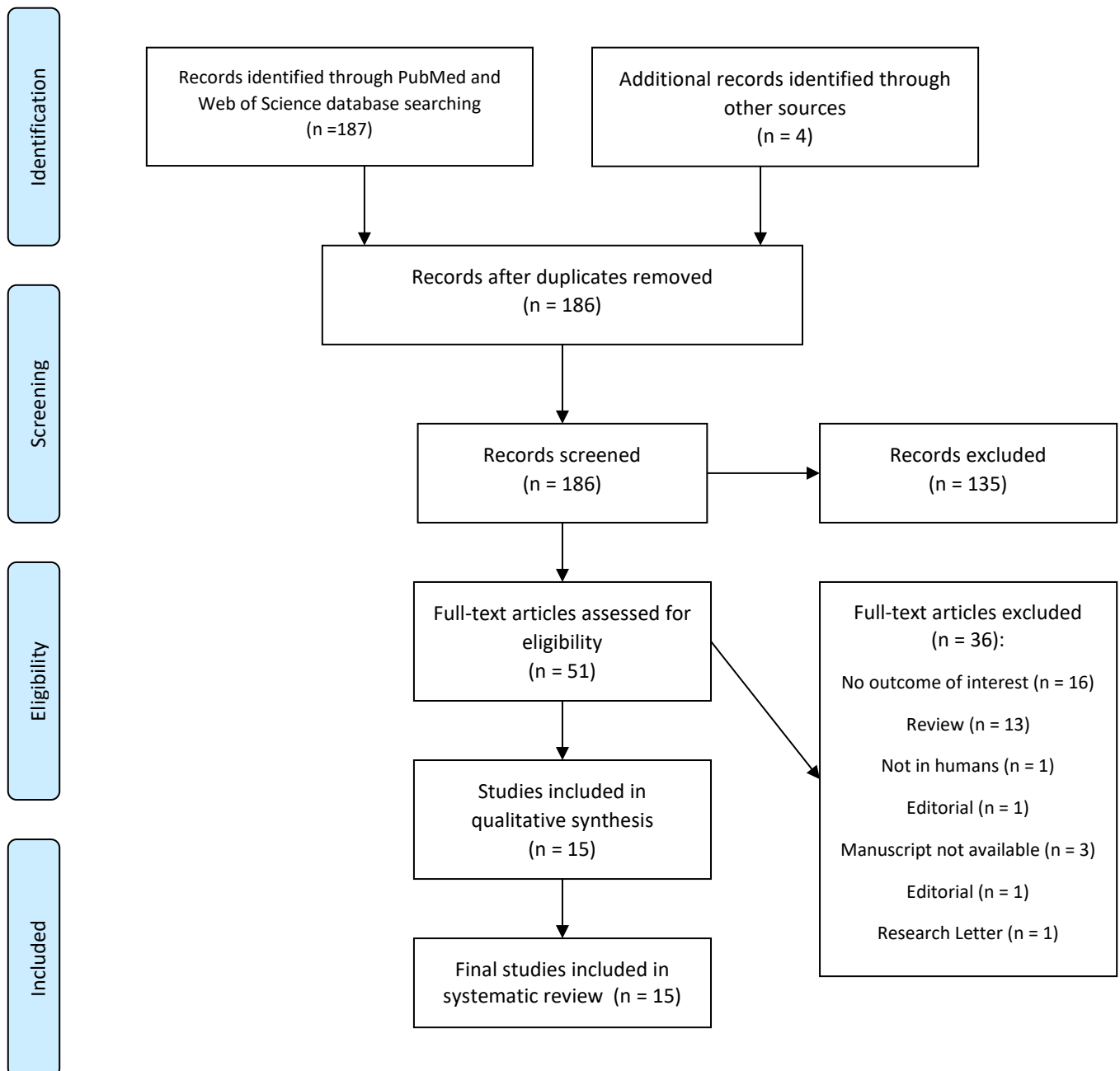


Table 1 – National Health Criteria

Criteria
1. Was the research question or objective in this paper clearly stated and appropriate?
2. Was the study population clearly specified and defined?
3. Did the authors include a sample size justification?
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?
5. 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?
6. Were the cases clearly defined and differentiated from controls?
7. 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?
8. Was there use of concurrent controls?
9. 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?
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?
11. Were the assessors of exposure/risk blinded to the case or control status of participants?
12. 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?

Table 2 - Quality Assessment

Reference	Quality Rating (Good, Fair, or Poor)	12 Questions Assessment
Antonatos, et al	Fair	(Y, Y, N, NR, Y, NY, NA, CD, N, Y, N, CD)
Cui et al	Fair	(Y, Y, N, Y, Y, Y, NA, CD, N, CD, Y, CD)
Lou et al	Fair	(Y, Y, N, Y, Y, Y, NA, CD, N, CD, Y, CD)
Shimony et al	Good	(Y, Y, N, N, Y, Y, Y, N, CD, CD, CD, Y)
Xie et al	Fair	(Y, Y, N, N, Y, Y, N, N, CD, CD, CD, CD)
Zemmour et al	Fair	(Y, Y, N, N, Y, Y, N, N, CD, CD, CD, CD)
Fujihara et al	Fair	(Y, Y, N, Y, Y, Y, NA, N, Y, Y, CD, CD)
Yokokawa et al	Good	(Y, Y, N, N, Y, Y, N, N, CD, CD, Y, CD)
Beck et al	Fair	(Y, Y, N, Y, Y, Y, CD, N, CD, CD, N, CD)
Bienkowski et al	Fair	(Y, Y, N, NA, Y, NA, NA, NA, CD, CD, CD, CD)
Gondi et al	Good	(Y, Y, Y, Y, Y, Y, CD, N, Y, Y, CD)
Khush et al	Good	(Y, Y, Y, N, Y, Y, CD, N, CD, CD, CD, N)
Macher et al	Fair	(Y, Y, N, NA, Y, NA, NA, NA, CD, CD, CD, CD)
Richmond et al	Good	(Y, Y, N, Y, Y, Y, CD, N, Y, Y, CD, Y)
Zangwill et al	Fair	(Y, Y, N, NA, Y, NA, NA, NA, CD, CD, CD, CD)

Y, Yes;
N, No;
CD, cannot determine;
NA, not applicable;
NR, not reported

Table 3 - Summary of the included articles

Serial no	Reference	Year	N. Patients	Country	Assay	Clinical Relevance	Main Findings
1	Antonatos, D <i>et al.</i>	2006	43	Greece	RT-PCR	Diagnosis and Prognosis	Cell-free DNA levels were also measured in 30 healthy controls. Log-transformed mean ($\pm$ SE) of maximum free DNA values in patients higher than controls (6873 ± 357 g.e./mL vs 4112 ± 234 g.e./mL, $P < 0.0001$). In conclusion, free DNA levels are significantly higher in patients with AMI than in controls and may play a role in the prognosis of these patients.
2	Cui, M <i>et al.</i>	2013	210	China	DNA-based Alu assay	Prognosis and Risk Stratification	ACS patients (median 2,285.0, interquartile range 916.4–4,857.3 ng/ml), especially in ST-segment elevation myocardial infarction patients (median 5,745.4, interquartile range 4,013.5–8,643.9 ng/ml), showed a significant increase in plasma cf-DNA concentrations compared with controls (healthy controls: median 118.3, interquartile range 81.1–221.1 ng/ml; Moreover, we found positive correlations between cfDNA and Gensini scoring and GRACE (Global Registry of Acute Coronary Events) scoring in ACS.
3	Lou, X <i>et al.</i>	2015	120	China	Alu based RT-PCR	Diagnosis and Prognosis	Plasma samples from patients with MI had higher concentration of cfDNA than the plasma samples from normal controls ($p < 0.01$). This Alu-based real-time PCR also showed better sensitivity and specificity for diagnosing MI when compared to troponin, creatine kinase and lactate dehydrogenase.
4	Shimony, A <i>et al.</i>	2010	63	Israel	Rapid fluorometric assay	Diagnosis	Peak CFD levels were significantly higher in patients compared with controls ($P = 0.001$) and correlated with peak levels of CK and troponin-T ($R = 0.79$, $P < 0.001$); $R = 0.65$, $P = 0.006$, respectively).
5	Zemmour, H <i>et al.</i>	2018	114 + subset from previous study for the sepsis section	Israel	Digital droplet PCR	Diagnosis and Monitoring	Plasma of healthy individuals contains essentially no cardiomyocyte cfDNA, consistent with minimal cardiac turnover. Patients with acute ST-elevation myocardial infarction show a robust cardiac cfDNA signal that correlates with levels of troponin and creatine phosphokinase (CPK), including the expected elevation-decay dynamics following coronary angioplasty.
6	Fujihara, J. <i>et al.</i>	2019	57 + 62 controls	Japan	Spectrophotometer	Diagnosis, Staging and Risk Stratification	Results revealed that the cfDNA concentrations in patients with MI and cardiac angina were significantly higher than that in healthy control subjects. Moreover, a cfDNA ratio of 150–200 bp/500–600 bp was significantly more prevalent in MI patients than in patients with other cardiac diseases (chest pain, cardiac angina, atrial fibrillation, and cardiac failure).
7	Xie, J. <i>et al.</i>	2018	130 + 30 controls	China	Spectrophotometer	Diagnosis and Prognosis	The results were highly correlative of CVD disease status. The mean concentration of cfDNA in patients with AMI was 5 folds higher during the onset of disease compared with healthy volunteers. Measuring cfDNA in patients with

CVD offers an alternative approach to monitor the disease and has potential clinical applications to identify high-risk individuals.

8	Yokokawa T. <i>et al.</i>	2019	32 HF patients + 28 controls	Japan	Quantitative PCR	Diagnosis and Prognosis	dPCR demonstrated that the copy numbers of unmethylated FAM101A locus of bisulfite-treated cfDNA were significantly increased in the heart failure group compared to the control group (0.99 [0.77 - 1.98] vs 0 [0 - 0.91] copies/mL, P = 0.003). Correlation analysis revealed that the levels of cardiomyocyte-specific cfDNA were significantly correlated with serum levels of high-sensitivity cardiac troponin I (r = 0.438, P = 0.012, Figure 1D) but not with BNP (r = 0.275, P = 0.058, Figure 1E), suggesting the elevated cardiomyocyte-specific cfDNA might be associated with enhanced cardiomyocyte death but not with high ventricular filling pressure.
9	Bienkowski M. <i>et al.</i>	2019	9 patients after heart transplant	Poland	ddPCR	Prognosis	There is an undeniable need for an alternative, non-invasive diagnostics of early transplant rejection. The investigation of ddcfDNA seems to be the promising choice. From 21 samples taken, 2 of them showed increased ddcfDNA. When compared with the results of the endomyocardial biopsy, only one of them showed possible histological signs of rejection (dense lymphocytic infiltration). The other one showed no signs of rejection in the biopsy and the increased levels of ddcfDNA were explained due to the fact that that patient had undergone cardiac tamponade and cardiac arrest a few days earlier.
10	Macher, H. <i>et al.</i>	2019	30 heart transplant patients	Spain	ddPCR	Prognosis	Patients without heart-related complications showed a high increase in the specific genomic marker levels during the first 24 h after transplantation that dropped to the basal levels on days 3–4 post-surgery. In contrast, patients with complications presented a significantly lagged decay pattern from day one after transplantation. A cfDNA increase was also observed during graft injury due to heart damage. These results suggest that cfDNA monitoring of transplanted patients may be a useful tool to detect and probably anticipate graft rejection.
11	Beck, J. <i>et al.</i>	2013	34 patients (8 heart transplants)	Germany	RT-PCR	Prognosis	Previous investigations in HTx recipients reported that the percentage of GcfDNA increased substantially during long-term treatment at least 3 months before biopsy-proven rejection. These data suggest that it may be possible to use such an assay for early detection of subclinical rejection, which could allow an individual adjustment of immunosuppressive therapy. Conventional tests used in heart transplantation (e.g., echocardiography and cardiac biopsies) are either nonspecific and insufficiently sensitive or invasive, respectively. There are no reliable laboratory biomarkers of HTx rejection.

12	Zangwill, S. <i>et al.</i>	2019	17 patients	USA	RT-PCR	Prognosis	In 17 patients with serial post-transplant samples, DF peaks in the first 2 days after transplant (3.5%, [1.9-10]%) and then declines toward baseline (0.27%, [0.19-0.52]%) by 6-9 days. There were 4 deaths in the first year among the 10 patients with complete sample sets, and 3 out of 4 who died had a late rise or blunted decline in donor fraction. Patients who died trended toward an elevated total cell-free DNA at 1 week (41.5, [34-65] vs 13.6, [6.2-22] P = .07). Patients without sustained decline in donor fraction and/or elevated total cell-free DNA at 1 week may have worse outcomes.
13	Gondi, K. <i>et al.</i>	2021	153 patients	USA	AlloSure CareDx Kit	Prognosis	We evaluated for frequency of EMB cancellation with ddcfDNA usage. A total of 153 OHT patients over a 13-month period underwent 495 combined GEP/ddcfDNA tests. 82.2% of ddcfDNA tests were below threshold. Above threshold results identified high-risk patients who developed AR. 378 combined tests ≥6 months post-OHT resulted in cancellation of 83.9% EMBs as opposed to 71.2% with GEP surveillance alone. Routine ddcfDNA testing alongside GEP testing yielded a significant reduction in EMB volume by re-classifying GEP (+) patients into a lower risk group, without reduction in AR detection.
14	Richmond M. <i>et al.</i>	2020	241 patients (146 <18 years and 95 ≥ 18 years)	USA	Quantitative RT-PCR	Prognosis	DF (donor fraction, defined as the ratio of cfDNA specific to the transplanted organ to the total amount of cfDNA present in the blood sample) in acute cellular rejection (ACR) 1R/2R (n = 15) was higher than ACR OR (n = 42) (p = 0.02); DF in antibody-mediated rejection pAMR1 (n = 8) and pAMR2 (n = 12) (p = 0.05) were higher than pAMRO (n = 466) (p = 0.04 and p = 0.05 respectively). The cell-free DNA DF holds promise as a non-invasive diagnostic test to rule out acute rejection in both adult and pediatric heart transplant populations.
15	Khush, K. <i>et al.</i>	2019	samples from 740 patients	USA	AlloSure CareDx Kit	Prognosis	In the study population of patients who had received an HT at least 55 days before enrollment, ddcfDNA testing detected AR with an AUC of 0.64 and provided an estimated NPV of 97.1% and PPV of 8.9%. We demonstrated that ddcfDNA levels are significantly higher in patients with AR compared with patients with no biopsy evidence of rejection.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page and paragraph/ table #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. - MANDATÓRIO	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. - SEGUIR RECOMENDAÇÕES DA REVISTA	Page 5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. - MANDATÓRIO <i>O rationale corresponde à justificação da importância da revisão sistemática</i>	Page 6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). - MANDATÓRIO	Page 6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. - FACULTATIVO	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. - MANDATÓRIO <i>É altamente recomendado, de acordo com as boas práticas da Cochrane, que não sejam aplicados critérios de exclusão baseados na língua e/ou data de publicação dos estudos.</i>	Page 7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. - MANDATÓRIO <i>Em consonância com as boas práticas da Cochrane, é mandatório que se verifique pesquisa em pelo menos duas bases de pesquisa bibliográfica (idealmente, deverão ser pesquisadas duas bases generalistas e uma específica da área). No caso de revisões sistemáticas de estudos experimentais/ensaio clínicos aleatorizados, é altamente recomendado que uma das bases pesquisadas corresponda à CENTRAL ou a bases de ensaios clínicos como a ClinicalTrials.gov.</i> <i>Estudos de revisão da literatura em que a pesquisa decorra numa única base de dados não serão classificados como revisões sistemáticas.</i>	Page 7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. - MANDATÓRIO <i>A query de pesquisa deve ser obrigatoriamente disponibilizada. A utilização de filtros de pesquisa da InterTASC é altamente recomendada (https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home)</i>	Page 7



PRISMA 2009 Checklist

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). – MANDATÓRIO <i>As fases de selecção dos estudos primários devem ser descritas. Em consonância com as boas práticas da Cochrane, é mandatório que o processo de selecção envolva duas fases (fase de rastreio, em que os registos são seleccionados por título e abstract, e fase de inclusão, na qual se procede à leitura integral dos full texts). Em cada uma destas fases, o processo de selecção deve mandatoriamente envolver dois investigadores actuando de forma independente.</i>	Page 7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. – MANDATÓRIO <i>Trata-se de descrever de que forma se procedeu à extracção de dados dos estudos primários. Em consonância com as boas práticas da Cochrane, tal processo deverá envolver dois investigadores de forma independente.</i>	Page 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. – MANDATÓRIO <i>Trata-se de descrever as variáveis para as quais foi obtida informação.</i>	Page 7
Risk of bias in individual studies / Risk of bias across studies	12/ 15	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. – MANDATÓRIO <i>Em todas as revisões sistemáticas, deverá existir um processo de avaliação da qualidade dos estudos primários. No caso de revisões sistemáticas de estudos experimentais/ensaiois clínicos aleatorizados, a aplicação dos critérios de risco de viés (Risk of Bias) da Cochrane é altamente recomendada. No caso de revisões sistemáticas de estudos observacionais, poderão ser seguidos os critérios ROBINS ou os critérios dos National Institutes of Health (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).</i>	Pages 18 – 19, Table 1 and 2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). – FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE	-
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. – FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. – FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. – MANDATÓRIO	Page 17, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. – MANDATÓRIO	Pages 20-22, Table 3
Risk of bias within and across studies	19/ 22	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). – MANDATÓRIO	Page 18 - 19, Table 1 and 2



PRISMA 2009 Checklist

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. – FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE	-
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. – FACULTATIVO. MANDATÓRIO APENAS SE FOR FEITA META-ANÁLISE	Pages 20-22, Table 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). – FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). – MANDATÓRIO	Pages 11 - 14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). – MANDATÓRIO	Page 13, paragraph 4
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. – MANDATÓRIO	Page 13, paragraph 5 and Page 14, paragraph 1
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. – SEGUIR RECOMENDAÇÕES DA REVISTA	Page 14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.



TABLE OF CONTENTS

•	Description	p.1
•	Impact Factor	p.1
•	Abstracting and Indexing	p.1
•	Editorial Board	p.1
•	Guide for Authors	p.7



ISSN: 0002-8703

DESCRIPTION

The *American Heart Journal* will consider for publication suitable articles on topics pertaining to the broad discipline of **cardiovascular disease**. Our goal is to provide the reader primary investigation, scholarly review, and opinion concerning the practice of **cardiovascular medicine**. We especially encourage [submission](#) of 3 types of reports that are not frequently seen in cardiovascular journals: negative clinical studies, reports on study designs, and studies involving the organization of medical care. The *Journal* does not accept individual case reports or original articles involving bench laboratory or animal research.

Benefits to authors

We also provide many author benefits, such as free PDFs, a liberal copyright policy, special discounts on Elsevier publications and much more. Please click [here](#) for more information on our [author services](#).

Please see our [Guide for Authors](#) for information on article submission. If you require any further information or help, please visit our [Support Center](#)

IMPACT FACTOR

2020: 4.749 © Clarivate Analytics Journal Citation Reports 2021

ABSTRACTING AND INDEXING

Scopus

EDITORIAL BOARD

Editor-in-Chief

Daniel Mark, Duke University School of Medicine, Durham, North Carolina, United States of America

Executive Editor

Patricia K. Hodgson, Duke Clinical Research Institute, Durham, North Carolina, United States of America

Managing Editor

Rebecca L. Hines, Duke Clinical Research Institute, Durham, North Carolina, United States of America

Quality and Innovations Editor

Melanie R. Daniels, Durham, North Carolina, United States of America

Journal Manager

Varun Ilangovan, Elsevier B.V., Chennai, India

Associate Editors

Andrew P. Ambrosy, Kaiser Permanente Northern California Division of Research, Oakland, California, United States of America

Sripal Bangalore, New York University Grossman School of Medicine, New York, New York, United States of America

Thomas M. Bashore, Duke University Medical Center, Durham, North Carolina, United States of America

Gerald S. Bloomfield, Duke University Division of Cardiology, Durham, North Carolina, United States of America

Melissa Burroughs-Pena, University of California San Francisco Division of Cardiology, San Francisco, California, United States of America

Derek Chew, University of Calgary, Calgary, Alberta, Canada

Jordana Cohen, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, United States of America

Melissa A. Daubert, Duke University Medical Center, Internal Medicine, Durham, North Carolina, United States of America

Adam DeVore, Duke University Medical Center, Durham, North Carolina, United States of America

Sean van Diepen, University of Alberta Hospital, Edmonton, Alberta, Canada

Justin Ezekowitz, University of Alberta Hospital, Edmonton, Alberta, Canada

Emil Fosbol, Copenhagen University Hospital Heart Centre, København, Denmark

J. Kevin Harrison, Duke University Division of Cardiology, Durham, North Carolina, United States of America

Paul A. Heidenreich, VA Palo Alto Health Care System, Palo Alto, California, United States of America

Connie N. Hess, University of Colorado - Anschutz Medical Campus, Aurora, Colorado, United States of America

Kevin D. Hill, Duke University, Durham, North Carolina, United States of America

Padma Kaul, University of Alberta, Edmonton, Alberta, Canada

Andrew Landstrom, Duke University Department of Pediatrics, Durham, North Carolina, United States of America

Angela Lowenstern, Vanderbilt University Division of Cardiovascular Medicine, Nashville, Tennessee, United States of America

Kenneth W. Mahaffey, Stanford University Department of Medicine, Stanford, California, United States of America

Robert McGarrah, Duke University Medical Center, Durham, North Carolina, United States of America

Michael Nanna, Yale University School of Medicine, Section of Cardiovascular Medicine, Branford, Connecticut, United States of America

Jonathan D. Newman, New York University Grossman School of Medicine, New York, New York, United States of America

Sudarshan Rajagopal, Duke University Medical Center, Durham, North Carolina, United States of America

Jennifer A. Rymer, Duke University Medical Center, Durham, North Carolina, United States of America

Nishant Shah, Duke University Division of Cardiology, Durham, North Carolina, United States of America

Matthew Sherwood, Inova Heart and Vascular Institute, Falls Church, Virginia, United States of America

Monique Starks, Duke Clinical Research Institute, Durham, North Carolina, United States of America

Emily P. Zeitler, Dartmouth Hitchcock Medical Center Department of Cardiology, Lebanon, New Hampshire, United States of America

Editorial Board

David Aguilar, The University of Texas Health Science Center at Houston, Houston, Texas, United States of America

Frank V. Aguirre, Prairie Heart Institute at Saint John's Hospital, Springfield, Illinois, United States of America

Tariq Ahmad, Yale School of Medicine, New Haven, Connecticut, United States of America

Hussein Al-Khalidi, Duke Clinical Research Institute, Durham, North Carolina, United States of America

Sana M. Al-Khatib, Duke Clinical Research Institute, Durham, North Carolina, United States of America

Rasha Al-Lamee, Imperial College London, London, United Kingdom

John H. Alexander, Duke Clinical Research Institute, Durham, North Carolina, United States of America

Karen P. Alexander, Duke Clinical Research Institute, Durham, North Carolina, United States of America

Larry A. Allen, University of Colorado Denver School of Medicine, Aurora, Colorado, United States of America

Kevin J. Anstrom, Duke Clinical Research Institute, Durham, North Carolina, United States of America

Paul W. Armstrong, University of Alberta, Edmonton, Alberta, Canada

Wilbert S. Aronow, New York Medical College, Valhalla, New York, United States of America

Alvaro Avezum, Oswaldo Cruz German Hospital, Sao Paulo, Brazil

Usman Baber, Mount Sinai Medical Center, Miami Beach, Florida, United States of America

Akshay Bagai, University of Toronto, Toronto, Ontario, Canada

Steven R. Bailey, The University of Texas Health Science Center at San Antonio, San Antonio, Texas, United States of America

Subhash Banerjee, The University of Texas Southwestern Medical Center, Dallas, Texas, United States of America

Gust H. Bardy, University of Washington Medical Center, Seattle, Washington, United States of America

Piers Barker, Duke University School of Medicine, Durham, North Carolina, United States of America

Gregory W. Barsness, Mayo Foundation for Medical Education and Research, Rochester, Minnesota, United States of America

Eric R. Bates, University of Michigan Michigan Medicine, Ann Arbor, Michigan, United States of America

Jeroen Joost Bax, Leiden University Medical Center Department of Cardiology, Leiden, Netherlands

Richard C. Becker, University of Cincinnati, Cincinnati, Ohio, United States of America

Jeffrey S. Berger, New York University, New York, New York, United States of America

Deepak L. Bhatt, Brigham and Women's Hospital, Boston, Massachusetts, United States of America

Kenneth Bilchick, UVA Health, Charlottesville, Virginia, United States of America

Philip F. Binkley, The Ohio State University Wexner Medical Center, Columbus, Ohio, United States of America

John A. Bittl, AdventHealth Ocala, Ocala, Florida, United States of America

Vera Bittner, The University of Alabama at Birmingham, Birmingham, Alabama, United States of America

Eric Boersma, Erasmus University Rotterdam, Rotterdam, Netherlands

Khadijah Breathett, University of Arizona, Advanced Heart Failure & Transplant, Division of Cardiology, Tucson, Arizona, United States of America

Sorin J. Brener, NewYork-Presbyterian Brooklyn Methodist Hospital, Brooklyn, New York, United States of America

Ralph G. Brindis, University of California San Francisco, San Francisco, California, United States of America

T. Jared Bunch, The University of Utah, Salt Lake City, Utah, United States of America

Javed Butler, Emory University School of Medicine, Atlanta, Georgia, United States of America

Alfred E. Buxton, Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States of America

Christopher P. Cannon, Brigham and Women's Hospital, Boston, Massachusetts, United States of America

Warren J. Cantor, Southlake Regional Health Centre, Newmarket, Ontario, Canada

Blase A. Carabello, Baylor College of Medicine, Houston, Texas, United States of America

Matthew Cavender, Brigham and Women's Hospital, Boston, Massachusetts, United States of America

Mark Y. Chan, National University Heart Centre, Singapore, Singapore

Tara A. Chang, Stanford University Division of Nephrology, Stanford, California, United States of America

W. Randolph Chitwood, Jr., East Carolina University, Greenville, North Carolina, United States of America

David J. Cohen, University of Missouri Kansas City, Kansas City, Missouri, United States of America

Marc Cohen, RMIT University School of Health and Biomedical Sciences, Bundoora, Australia

Mauricio G. Cohen, University of Miami School of Medicine, Miami, Florida, United States of America

Stuart J. Connolly, Hamilton Health Sciences, , Canada

Patricia Cowper, Duke University, Durham, North Carolina, United States of America

Anne B. Curtis, University at Buffalo, Buffalo, New York, United States of America

Abdulla Damluji, Johns Hopkins University, Baltimore, Maryland, United States of America

James P. Daubert, Duke University Health System, Durham, North Carolina, United States of America

Charles J. Davidson, Northwestern Medical Faculty Foundation, Chicago, Illinois, United States of America

J. Michael DiMaio, Baylor Scott & White Health, Dallas, Texas, United States of America

Pamela S. Douglas, Duke University, Durham, North Carolina, United States of America

Shannon Dunlay, Mayo Foundation for Medical Education and Research, Rochester, Minnesota, United States of America

Vladimir Dzavik, University Health Network, Toronto, Ontario, Canada

Kim Eagle, University of Michigan Michigan Medicine, Ann Arbor, Michigan, United States of America

Zubin Eapen, Duke University School of Medicine, Durham, North Carolina, United States of America

Eric Eisenstein, Duke Clinical Research Institute, Durham, North Carolina, United States of America

Ismail El-Hamamsy, University of Montreal, Montreal, Quebec, Canada

Islam Y. Elgendy, Weill Cornell Medicine - Qatar, Doha, Qatar

Kenneth A. Ellenbogen, Virginia Commonwealth University Medical Center, Richmond, Virginia, United States of America

Stephen G. Ellis, Cleveland Clinic, Cleveland, Ohio, United States of America

Alexander Fanaroff, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America

David P. Faxon, Brigham and Women's Hospital, Boston, Massachusetts, United States of America

G. Michael Felker, Duke University School of Medicine, Durham, North Carolina, United States of America

T. Bruce Ferguson, Jr., East Carolina University, Greenville, North Carolina, United States of America

Jerome L. Fleg, National Heart Lung and Blood Institute, Bethesda, Maryland, United States of America

Gregg C. Fonarow, University of California Los Angeles, Los Angeles, California, United States of America

Christopher Fordyce, Duke University, Durham, North Carolina, United States of America

James Freeman, Yale School of Medicine, New Haven, Connecticut, United States of America

John K. French, Liverpool Hospital, Liverpool, Australia

Daniel J. Friedman, Duke University, Durham, North Carolina, United States of America

Marat Fudim, Duke Clinical Research Institute, Durham, North Carolina, United States of America

Thomas C. Gerber, Mayo Clinic Rochester, Rochester, Minnesota, United States of America

Bernard J. Gersh, Mayo Clinic Rochester, Rochester, Minnesota, United States of America

Jeffrey B. Geske, Mayo Foundation for Medical Education and Research, Rochester, Minnesota, United States of America

Jalal Ghali, Morehouse School of Medicine, Atlanta, Georgia, United States of America

Raymond J. Gibbons, Mayo Foundation for Medical Education and Research, Rochester, Minnesota, United States of America

C. Michael Gibson, Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States of America

Ian Gilchrist, Penn State Health Milton S Hershey Medical Center, Hershey, Pennsylvania, United States of America

Robert P. Giugliano, Brigham and Women's Hospital, Boston, Massachusetts, United States of America

Donald D. Glower, Duke University, Durham, North Carolina, United States of America

Andrew M. Goldsweig, University of Nebraska Medical Center, Omaha, Nebraska, United States of America

Bulent Gorenek, Eskisehir Osmangazi University, Eskisehir, Turkey

Christopher B. Granger, Duke University, Durham, North Carolina, United States of America

Jennifer Green, Duke University Medical Center, Division of Endocrinology, Durham, North Carolina, United States of America

Anna Gundlund, Herlev Hospital, Herlev, Denmark

Paul A. Gurbel, Inova Heart and Vascular Institute, Falls Church, Virginia, United States of America

Hitinder S. Gurm, University of Michigan Michigan Medicine, Ann Arbor, Michigan, United States of America

John R. Guyton, Duke University Hospital, Durham, North Carolina, United States of America

Bradley Hammill, Duke University, Durham, North Carolina, United States of America

Frank E. Harrell, Jr., Vanderbilt University School of Medicine, Nashville, Tennessee, United States of America

Robert A. Harrington, Stanford University School of Medicine, Stanford, California, United States of America

David Hasdai, Rabin Medical Center Davidoff Center, Petah Tikva, Israel

Edward P. Havranek, University of Colorado, Denver, Colorado, United States of America

Robert C. Hendel, University of Miami School of Medicine, Miami, Florida, United States of America

Timothy D. Henry, Cedars-Sinai Heart Institute, Los Angeles, California, United States of America

Adrian F. Hernandez, Duke Clinical Research Institute, Durham, North Carolina, United States of America

Charles A. Herzog, Chronic Disease Research Group, Minneapolis, Minnesota, United States of America

Paul Hess, University of Colorado - Anschutz Medical Campus, Aurora, Colorado, United States of America

James A. Hill, University of Florida College of Medicine, Gainesville, Florida, United States of America

Mark A. Hlatky, Stanford University, Stanford, California, United States of America

Judith S. Hochman, New York University Grossman School of Medicine, New York, New York, United States of America

Dajuanicia Holmes, Duke Clinical Research Institute, Durham, North Carolina, United States of America

David R. Holmes, Jr., Mayo Foundation for Medical Education and Research, Rochester, Minnesota, United States of America

Michael P. Hudson, Henry Ford Hospital, Detroit, Michigan, United States of America

Larry Jackson, Duke University School of Medicine, Durham, North Carolina, United States of America

Alice K. Jacobs, Boston Medical Center, Boston, Massachusetts, United States of America

Stefan James, Uppsala University Hospital, Uppsala, Sweden

James L. Januzzi, Jr., Harvard Medical School, Boston, Massachusetts, United States of America

Marc E. Jolicoeur, University of Montreal, Montreal Heart Institute, Montreal, Quebec, Canada

William Schuyler Jones, Duke University, Durham, North Carolina, United States of America

Andreas Kalogeropoulos, Stony Brook University School of Medicine, Division of Cardiology, Stony Brook, New York, United States of America

David E. Kandzari, Piedmont Heart Institute, Atlanta, Georgia, United States of America

Adnan Kastrati, Technical University of Munich, Munich, Germany

Dean J. Kereiakes, Christ Hospital, Cincinnati, Ohio, United States of America

Morton J. Kern, VA Long Beach Healthcare System, Long Beach, California, United States of America

Prateeti Khazanie, University of Colorado - Anschutz Medical Campus, Aurora, Colorado, United States of America

Michel G. Khouri, Duke University, Durham, North Carolina, United States of America

Ajay J. Kirtane, Columbia University Irving Medical Center, New York, New York, United States of America

Neal S. Kleiman, Houston Methodist DeBakey Heart & Vascular Center, Houston, Texas, United States of America

George J. Klein, London Health Sciences Centre, London, Ontario, Canada

Ajar Kochar, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts, United States of America

Robb Kociol, Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States of America

Dhaval Kolte, Massachusetts General Hospital, Boston, Massachusetts, United States of America

Richard A. Krasuski, Duke University School of Medicine, Durham, North Carolina, United States of America

William E. Kraus, Duke University, Durham, North Carolina, United States of America

Joseph Ladapo, University of California Los Angeles David Geffen School of Medicine, Los Angeles, California, United States of America

Gervasio A. Lamas, The Mount Sinai Hospital, New York, New York, United States of America

Kerry L. Lee, Duke University School of Medicine, Durham, North Carolina, United States of America

Thomas H. Lee, Jr., Harvard University, Cambridge, Massachusetts, United States of America

Sergio Leonardi

Jennifer S. Li, Duke University, Durham, North Carolina, United States of America
A. Michael Lincoff, Cleveland Clinic, Cleveland, Ohio, United States of America
Gregory Y.H. Lip, University of Liverpool, Liverpool, United Kingdom
James E. Lock, Boston Children's Hospital, Boston, Massachusetts, United States of America
Yuliya Likhnygina, Duke University, Durham, North Carolina, United States of America
Renato D. Lopes, Duke University Medical Center, Durham, North Carolina, United States of America
Jared William Magnani, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America
Thomas H. Marwick, University of Tasmania Menzies Institute for Medical Research, Hobart, Australia
Frederick A. Masoudi, University of Colorado - Anschutz Medical Campus, Aurora, Colorado, United States of America
Charles Maynard, University of Washington, Seattle, Washington, United States of America
Darren K. McGuire, The University of Texas Southwestern Medical Center, Dallas, Texas, United States of America
Roxana Mehran, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America
Rajendra Mehta, Duke Clinical Research Institute, Durham, North Carolina, United States of America
Venugopal Menon, Cleveland Clinic, Cleveland, Ohio, United States of America
George A. Mensah, National Heart Lung and Blood Institute, Bethesda, Maryland, United States of America
Robert E. Michler, Montefiore Medical Center Department of Cardiothoracic and Vascular Surgery, Bronx, New York, United States of America
Julie M. Miller, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America
David J. Moliterno, University of Kentucky College of Medicine, Lexington, Kentucky, United States of America
Fred Morady, University of Michigan Michigan Medicine, Ann Arbor, Michigan, United States of America
Maria Mori Brooks, University of Pittsburgh Department of Epidemiology, Pittsburgh, Pennsylvania, United States of America
David Morrow, Brigham and Women's Hospital, Boston, Massachusetts, United States of America
Joseph Brent Muhlestein, The University of Utah, Salt Lake City, Utah, United States of America
Debabrata Mukherjee, Texas Tech University System, Lubbock, Texas, United States of America
Brahmajee Nallamothu, University of Michigan, Ann Arbor, Michigan, United States of America
Ann Marie Navar, The University of Texas Southwestern Medical Center, Dallas, Texas, United States of America
L. Kristin Newby, Duke University School of Medicine, Durham, North Carolina, United States of America
Peter A. Noseworthy, Mayo Foundation for Medical Education and Research, Rochester, Minnesota, United States of America
Emily C. O'Brien, Duke University, Durham, North Carolina, United States of America
Sean M. O'Brien, Duke University, Durham, North Carolina, United States of America
Michael O'Byrne, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, United States of America
Christopher M. O'Connor, Duke University School of Medicine, Durham, North Carolina, United States of America
Michelle O'Shaughnessy, Stanford University, Stanford, California, United States of America
E. Magnus Ohman, Duke University School of Medicine, Durham, North Carolina, United States of America
Peter M. Okin, Cornell University, Ithaca, New York, United States of America
Brian Olshansky, The University of Iowa Hospitals and Clinics, Iowa City, Iowa, United States of America
Catherine M. Otto, University of Washington, Seattle, Washington, United States of America
Eileen O'Meara, Montreal Heart Institute, Montreal, Quebec, Canada
Douglas L. Packer, Mayo Foundation for Medical Education and Research, Rochester, Minnesota, United States of America
Richard L. Page, University of Wisconsin-Madison, Madison, Wisconsin, United States of America
Neha Pagidipati, Duke University, Durham, North Carolina, United States of America
Chetan Patel, Duke University School of Medicine, Durham, North Carolina, United States of America
Manesh R. Patel, Duke University, Durham, North Carolina, United States of America
Carl Pepine, University of Florida College of Medicine, Gainesville, Florida, United States of America
John L. Petersen II, Swedish Medical Center, Seattle, Washington, United States of America
Eric D. Peterson, Duke University, Durham, North Carolina, United States of America
Pamela N. Peterson, University of Colorado, Denver, Colorado, United States of America
Marc A. Pfeffer, Harvard Medical School, Boston, Massachusetts, United States of America
Jonathan P. Piccini, Duke Clinical Research Institute, Durham, North Carolina, United States of America
Louise Pilote, McGill University, Montreal, Quebec, Canada
Bertram Pitt, University of Michigan Michigan Medicine, Ann Arbor, Michigan, United States of America
Sean D. Pokorney, Duke University, Durham, North Carolina, United States of America
Jeanne E. Poole, University of Washington Division of Cardiology, Seattle, Washington, United States of America
Jeffrey J. Popma, Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States of America
Thomas Povsic, Duke Clinical Research Institute, Durham, North Carolina, United States of America
Eric N. Prystowsky, The Cancer Care Group, Indianapolis, Indiana, United States of America
Alexandre Schaan de Quadros, Cardiological Institute, PORTO ALEGRE, Brazil
Paolo Raggi, Emory University School of Medicine, Atlanta, Georgia, United States of America
Sunil V. Rao, Durham VA Medical Center, Durham, North Carolina, United States of America

Harmony Reynolds, New York University Grossman School of Medicine, New York, New York, United States of America

Vera H. Rigolin, Northwestern University Feinberg School of Medicine, Chicago, Illinois, United States of America

Joseph G. Rogers, Duke University, Durham, North Carolina, United States of America

Melvyn Rubenfire, University of Michigan, Ann Arbor, Michigan, United States of America

John S. Rumsfeld, University of Colorado - Anschutz Medical Campus, Aurora, Colorado, United States of America

Thomas Ryan, The Ohio State University, Columbus, Ohio, United States of America

Jennifer A. Rymer, Duke University Medical Center, Durham, North Carolina, United States of America

Zainab Samad, The Aga Khan University Medical College Pakistan, Karachi, Pakistan

Gillian D. Sanders-Schmidler

Alex Sandhu, Falk Cardiovascular Research Center, Stanford, California, United States of America

Hartzell V. Schaff, Mayo Foundation for Medical Education and Research, Rochester, Minnesota, United States of America

Kevin A. Schulman, Duke University, Durham, North Carolina, United States of America

Svati H. Shah, Duke University, Durham, North Carolina, United States of America

Abhinav Sharma, McGill University Health Centre, Montreal, Quebec, Canada

Leslee Shaw, Emory University, Atlanta, Georgia, United States of America

Chetan Shenoy, University of Minnesota Twin Cities, Minneapolis, Minnesota, United States of America

Adhir Shroff, University of Illinois at Chicago, Division of Cardiology, Chicago, Illinois, United States of America

Nathaniel R Smilowitz, NYU Langone Health, New York, New York, United States of America

Benjamin Steinberg, The University of Utah, Salt Lake City, Utah, United States of America

Steven R. Steinhubl, Geisinger Health, Danville, Pennsylvania, United States of America

Lynne W. Stevenson, Brigham and Women's Hospital, Boston, Massachusetts, United States of America

William G. Stevenson, Harvard Medical School, Boston, Massachusetts, United States of America

Carla A. Sueta

Nadia Sutton, University of Michigan, Ann Arbor, Michigan, United States of America

Toru Suzuki, University of Leicester, Leicester, United Kingdom

W.H. Wilson Tang, Cleveland Clinic, Cleveland, Ohio, United States of America

Allen J. Taylor, MedStar Georgetown University Hospital, Washington, District of Columbia, United States of America

James E. Tcheng, Duke University, Durham, North Carolina, United States of America

Laine Thomas, Duke University, Durham, North Carolina, United States of America

Mintu Turakhia, Stanford University School of Medicine, Stanford, California, United States of America

Jacob A. Udell

Anne Marie Valente, Boston Children's Hospital, Department of Cardiology, Boston, Massachusetts, United States of America

Frans J.J. Van de Werf, KU Leuven University Hospitals Leuven, Leuven, Belgium

Sreekanth Vemulapalli

Hector O. Ventura, Ochsner Medical Center John Ochsner Heart and Vascular Institute, New Orleans, Louisiana, United States of America

Mladen I. Vidovich, University of Illinois at Chicago, Jesse Brown VA Medical Center, Chicago, Illinois, United States of America

Lars Wallentin

Andrew Wang, Duke University, Durham, North Carolina, United States of America

Tracy Y. Wang

Jeffrey Washam, Duke Heart Center, Durham, North Carolina, United States of America

W. Douglas Weaver, Henry Ford Hospital, Detroit, Michigan, United States of America

William S. Weintraub, Christiana Care Health System, Newark, Delaware, United States of America

Cynthia M. Westerhout, University of Alberta, Edmonton, Alberta, Canada

David J. Whellan, Thomas Jefferson University, Philadelphia, Pennsylvania, United States of America

Harvey D. White, Auckland, New Zealand

Janet Wittes, Statistics Collaborative, Inc., Washington, District of Columbia, United States of America

Clyde W. Yancy, Northwestern University, Evanston, Illinois, United States of America

James B. Young, Cleveland Clinic, Cleveland, Ohio, United States of America

GUIDE FOR AUTHORS

Your Paper Your Way

We now differentiate between the requirements for new and revised submissions. You may choose to submit your manuscript as a single Word or PDF file to be used in the refereeing process. Only when your paper is at the revision stage, will you be requested to put your paper in to a 'correct format' for acceptance and provide the items required for the publication of your article.

To find out more, please visit the Preparation section below.

Editor in Chief: **Daniel B. Mark, MD, MPH**

Executive Editor: **Patricia K. Hodgson**

Managing Editor: **Rebecca L. Hines** E-mail: AHJ@dm.duke.edu

American Heart Journal

Duke Clinical Research Institute

Telephone: 919-668-5948

Fax: 919-668-7046

E-mail: AHJ@dm.duke.edu

Information for Authors

All articles except letters to the editor and supplements must be submitted online at <https://www.editorialmanager.com/amhj/default.aspx>. The *American Heart Journal* no longer accepts submissions by mail. Letters to the editor must be submitted directly to Rebecca L. Hines, Managing Editor, at AHJ@dm.duke.edu. Supplement proposals must be submitted to Craig Smith at C.Smith@Elsevier.com. The Journal will consider for publication suitable articles on topics pertaining to the broad discipline of cardiovascular disease. Our goal is to provide the reader with primary investigation, scholarly review, and opinion concerning the practice of cardiovascular medicine. We especially encourage submission of 3 types of reports that are not frequently seen in cardiovascular journals: negative clinical studies, reports on study designs, and studies involving the organization of medical care. (For more information, see "[What We Publish in the American Heart Journal and Why](#)," by Daniel B. Mark, MD, MPH, [Am Heart J 2007;154:1-2].) The Journal does not accept individual case reports or original articles involving bench laboratory or animal research. All communications relating to the editorial management of the Journal should be sent to Rebecca L. Hines, Managing Editor, at AHJ@dm.duke.edu.

Editorial policies. Statements and opinions expressed in the Journal are those of the author(s) and not necessarily those of the Editor(s) or publisher, and the Editor(s) and publisher disclaim any responsibility or liability for such material. Neither the Editor(s) nor the publisher guarantees, warrants, or endorses any product or service advertised in this publication; neither do they guarantee any claim made by the manufacturer of such product or service. In accordance with the Copyright Act of 1976, which became effective January 1, 1978, the following statement signed by all authors must accompany each manuscript accepted for publication: "The undersigned author(s) transfer all copyright ownership of the manuscript [title of article] to Elsevier Inc., in the event the work is published. The undersigned warrant(s) that the article is original, does not infringe upon any copyright or other proprietary right of any third party, is not under consideration by another journal, and has not been published previously." When a manuscript is accepted for publication, the Copyright Release Form will be issued to authors from the publisher.

Review. All articles are pre-screened by the Editors and Associate Editors. Papers felt not to be competitive for publication or papers not consistent with the editorial priorities of the *American Heart Journal* will be returned to the authors without review within 4 weeks of submission. All other articles are reviewed by external referees. Acceptance is based on significance, originality, and validity of the material. If the article is accepted for publication, editorial revisions may be made to aid clarity and understanding without altering the meaning.

Sections. The following sections are established features of the Journal. To ensure that the manuscript is considered for one of the following sections, the name of the intended section should appear at the top of the title page.

Clinical Investigations. Original, in-depth clinical investigations.

Curriculum in Cardiology. Concise, comprehensive, contemporary articles presenting core, updated information necessary for the continuing medical education of the modern clinical cardiologist.

Progress in Cardiology. Concise and comprehensive articles devoted to innovative new areas of development in cardiovascular diseases important to the clinical cardiologist.

Trial Designs. Efficient but thorough descriptions of study protocols, including the conceptual issues underlying the hypotheses, the methodology, and planned analysis of a trial. An important part of the evaluation of trial design papers pertains to the likely ability of the investigators to complete the trial as planned. Papers should include target sample size information along with a timeline for enrollment and follow-up. If the trial has already begun enrollment, provide number of patients enrolled as of the date of manuscript submission.

Research Letters. Short, original research articles or brief reports of up to 1500 words and with up to 12 references. May contain up to 3 figures or tables. A short abstract of three sentences or less describing the objective of the letter is required. Online supplemental material is permitted, particularly for additional relevant methods or results.

Letters to the Editor. Brief letters or notes to the Editor regarding published material or information of timely interest. Letters to the Editor should concern only articles that have been published recently in the Journal. A response to the letter will be requested from the authors of the article in question, and both the letter and the response will be published together. Letters to the Editor must be submitted by e-mail to Rebecca L. Hines, Managing Editor, at AHJ@dm.duke.edu. **Letters will be published on the Journal's Website only.**

Editorials. Brief, substantiated commentary on special subjects.

Supplements. Symposia are considered for publication on the basis of importance of topic, expertise of participants, and scientific quality of articles presented. All supplements undergo peer review. Proprietary sponsorship must be indicated. Supplement proposals must be submitted by e-mail to Craig Smith at C.Smith@Elsevier.com.

Submission checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:

- E-mail address
- Full postal address

All necessary files have been uploaded:

Manuscript:

- Include keywords
- All figures (include relevant captions)
- All tables (including titles, description, footnotes)
- Ensure all figure and table citations in the text match the files provided
- Indicate clearly if color should be used for any figures in print

Graphical Abstracts / Highlights files (where applicable)

Supplemental files (where applicable)

Further considerations

- Manuscript has been 'spell checked' and 'grammar checked'
- All references mentioned in the Reference List are cited in the text, and vice versa
- Permission has been obtained for use of copyrighted material from other sources (including the Internet)
- A competing interests statement is provided, even if the authors have no competing interests to declare
- Journal policies detailed in this guide have been reviewed
- Referee suggestions and contact details provided, based on journal requirements

For further information, visit our [Support Center](#).

BEFORE YOU BEGIN

Declaration of interest

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential competing interests include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. Authors must disclose any interests in two places: 1. A summary declaration of interest statement in the title page file (if double anonymized) or the manuscript file (if single anonymized). If there are no interests to declare then please state this: 'Declarations of interest: none'. 2. Detailed disclosures as part of a separate Declaration of Interest form, which forms part of the journal's official records. It is important for potential interests to be declared in both places and that the information matches. [More information](#).

Submission declaration

Submission of an article implies that the work described has not been published previously (except in the form of an abstract, a published lecture or academic thesis, see '[Multiple, redundant or concurrent publication](#)' for more information), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Preprints

Please note that [preprints](#) can be shared anywhere at any time, in line with Elsevier's [sharing policy](#). Sharing your preprints e.g. on a preprint server will not count as prior publication (see '[Multiple, redundant or concurrent publication](#)' for more information).

Use of inclusive language

Inclusive language acknowledges diversity, conveys respect to all people, is sensitive to differences, and promotes equal opportunities. Content should make no assumptions about the beliefs or commitments of any reader; contain nothing which might imply that one individual is superior to another on the grounds of age, gender, race, ethnicity, culture, sexual orientation, disability or health condition; and use inclusive language throughout. Authors should ensure that writing is free from bias, stereotypes, slang, reference to dominant culture and/or cultural assumptions. We advise to seek gender neutrality by using plural nouns ("clinicians, patients/clients") as default/wherever possible to avoid using "he, she," or "he/she." We recommend avoiding the use of descriptors that refer to personal attributes such as age, gender, race, ethnicity, culture, sexual orientation, disability or health condition unless they are relevant and valid. When coding terminology is used, we recommend to avoid offensive or exclusionary terms such as "master", "slave", "blacklist" and "whitelist". We suggest using alternatives that are more appropriate and (self-) explanatory such as "primary", "secondary", "blocklist" and "allowlist". These guidelines are meant as a point of reference to help identify appropriate language but are by no means exhaustive or definitive.

Author contributions

For transparency, we encourage authors to submit an author statement file outlining their individual contributions to the paper using the relevant CRediT roles: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing. Authorship statements should be formatted with the names of authors first and CRediT role(s) following. [More details and an example](#).

Registration of randomized clinical trials. Any manuscript submitted to the Journal that concerns the design or results of a randomized clinical trial must include the registration site (such as www.clinicaltrials.gov) and the registration number in the Methods section.

Article transfer service

This journal is part of our Article Transfer Service. This means that if the Editor feels your article is more suitable in one of our other participating journals, then you may be asked to consider transferring the article to one of those. If you agree, your article will be transferred automatically on your behalf with no need to reformat. Please note that your article will be reviewed again by the new journal. [More information](#).

Copyright

Upon acceptance of an article, authors will be asked to complete a 'Journal Publishing Agreement' (see [more information](#) on this). An e-mail will be sent to the corresponding author confirming receipt of the manuscript together with a 'Journal Publishing Agreement' form or a link to the online version of this agreement.

Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. [Permission](#) of the Publisher is required for resale or distribution outside the institution and for all other derivative works, including compilations and translations. If excerpts from other copyrighted works are included, the author(s) must obtain written permission from the copyright owners and credit the source(s) in the article. Elsevier has [preprinted forms](#) for use by authors in these cases.

For gold open access articles: Upon acceptance of an article, authors will be asked to complete a 'License Agreement' ([more information](#)). Permitted third party reuse of gold open access articles is determined by the author's choice of [user license](#).

Author rights

As an author you (or your employer or institution) have certain rights to reuse your work. [More information](#).

Elsevier supports responsible sharing

Find out how you can [share your research](#) published in Elsevier journals.

Open access

Please visit our [Open Access page](#) for more information.

Open access. This journal offers you the option of making your article freely available via the ScienceDirect platform. To prevent any conflict of interest, you can make this choice only after receiving notification that your article has been accepted for publication. The fee of \$3,250 excludes taxes and other potential author fees such as color charges. In some cases, institutions and funding bodies have entered into agreement with Elsevier to meet these fees on behalf of their authors. Details of these agreements are available at <https://www.elsevier.com/fundingbodies>. Authors of accepted articles who wish to take advantage of this option should complete and submit the order form (available at <https://www.elsevier.com/locate/openaccessform.pdf>). Whatever access option you choose, you retain many rights as an author, including the right to post a revised personal version of your article on your own website. More information can be found here: <https://www.elsevier.com/authorsrights>.

Elsevier Researcher Academy

[Researcher Academy](#) is a free e-learning platform designed to support early and mid-career researchers throughout their research journey. The "Learn" environment at Researcher Academy offers several interactive modules, webinars, downloadable guides and resources to guide you through the process of writing for research and going through peer review. Feel free to use these free resources to improve your submission and navigate the publication process with ease.

Human research. Authors should identify that informed consent was obtained when applicable. The manuscript should also include the notation that the study was approved by the institutional committee on human research. Photographs of identifiable persons must be accompanied by signed releases showing informed consent. These should be included at the time of manuscript submission.

Submission

Our online submission system guides you stepwise through the process of entering your article details and uploading your files. The system converts your article files to a single PDF file used in the peer-review process. Editable files (e.g., Word, LaTeX) are required to typeset your article for final publication. All correspondence, including notification of the Editor's decision and requests for revision, is sent by e-mail.

Submit your article

Please submit your article via <https://www.editorialmanager.com/amhj/default.aspx>.

Preparation of manuscripts. Only original manuscripts will be considered for publication. Correct preparation of the manuscript by the authors will expedite the review and publication procedures. Please note the following requirements. Following the instructions for online submission

at <https://www.editorialmanager.com/amhj/default.aspx>, the article, including all tables, should be formatted in Microsoft Word. The use of appropriate subheadings throughout the body of the text (Methods, Results, and Discussion sections) is required. Figures and illustrations must also be submitted electronically as separate files. File specifications are listed below in "Illustrations, figures, and legends."

NEW SUBMISSIONS

Submission to this journal proceeds totally online and you will be guided stepwise through the creation and uploading of your files. The system automatically converts your files to a single PDF file, which is used in the peer-review process.

As part of the Your Paper Your Way service, you may choose to submit your manuscript as a single file to be used in the refereeing process. This can be a PDF file or a Word document, in any format or layout that can be used by referees to evaluate your manuscript. It should contain high enough quality figures for refereeing. If you prefer to do so, you may still provide all or some of the source files at the initial submission. Please note that individual figure files larger than 10 MB must be uploaded separately.

References

There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume number/book chapter and the article number or pagination must be present. Use of DOI is highly encouraged. The reference style used by the journal will be applied to the accepted article by Elsevier at the proof stage. Note that missing data will be highlighted at proof stage for the author to correct.

Formatting requirements

There are no strict formatting requirements but all manuscripts must contain the essential elements needed to convey your manuscript, for example Abstract, Keywords, Introduction, Materials and Methods, Results, Conclusions, Artwork and Tables with Captions.

If your article includes any Videos and/or other Supplementary material, this should be included in your initial submission for peer review purposes.

Divide the article into clearly defined sections.

Figures and tables embedded in text

Please ensure the figures and the tables included in the single file are placed next to the relevant text in the manuscript, rather than at the bottom or the top of the file. The corresponding caption should be placed directly below the figure or table.

Peer review

This journal operates a single anonymized review process. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of two independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. Editors are not involved in decisions about papers which they have written themselves or have been written by family members or colleagues or which relate to products or services in which the editor has an interest. Any such submission is subject to all of the journal's usual procedures, with peer review handled independently of the relevant editor and their research groups. [More information on types of peer review.](#)

REVISED SUBMISSIONS

Use of word processing software

Regardless of the file format of the original submission, at revision you must provide us with an editable file of the entire article. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the [Guide to Publishing with Elsevier](#)). See also the section on Electronic artwork.

To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Style. Manuscripts must conform to acceptable English usage. Standard abbreviations should be used consistently throughout the article. Abbreviations should be spelled out the first time they appear in the text and followed in parentheses by the abbreviation. Consult the latest editions of *Scientific Style and Format* by the Council of Biology Editors, *The Chicago Manual of Style* by The University of Chicago Press, or the AMA's *Manual of Style*, 9th edition, for current usage.

Pagination. Begin numbering with the title page as page 1, the structured abstract page as page 2, and continue throughout the references, figure legends, and tables. Place page numbers on each page.

Title page. The title page should be typed double-spaced and should include the title, authors' full names, highest earned academic degrees, institutional affiliations and location, and a short, abbreviated title of 40 characters or fewer. Designate one author (provide address, business telephone and fax numbers, and e-mail address) to receive correspondence, galley proofs, and reprint requests. This journal publishes author-accepted manuscripts online; therefore, do not include in the manuscript any information such as home telephone number that you do not wish to be made publicly available.

Highlights

Highlights are mandatory for this journal as they help increase the discoverability of your article via search engines. They consist of a short collection of bullet points that capture the novel results of your research as well as new methods that were used during the study (if any). Please have a look at the examples here: [example Highlights](#).

Highlights should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

Structured abstract. Each article must include a structured abstract of no more than 250 words. Use the following headings for sections of the abstract: Background, Methods, Results, Conclusions. The abstract may not contain data not presented in the manuscript. For review articles and trial designs, in place of a structured abstract, please provide a summary abstract paragraph (maximum word count 250 words). If abstract subheadings are not appropriate, they may be omitted.

Graphical abstract

Although a graphical abstract is optional, its use is encouraged as it draws more attention to the online article. The graphical abstract should summarize the contents of the article in a concise, pictorial form designed to capture the attention of a wide readership. Graphical abstracts should be submitted as a separate file in the online submission system. Image size: Please provide an image with a minimum of 531 × 1328 pixels (h × w) or proportionally more. The image should be readable at a size of 5 × 13 cm using a regular screen resolution of 96 dpi. Preferred file types: TIFF, EPS, PDF or MS Office files. You can view [Example Graphical Abstracts](#) on our information site.

Authors can make use of Elsevier's [Illustration Services](#) to ensure the best presentation of their images and in accordance with all technical requirements.

Acknowledgements

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

Footnotes

Footnotes should be used sparingly. Number them consecutively throughout the article. Many word processors build footnotes into the text, and this feature may be used. Should this not be the case, indicate the position of footnotes in the text and present the footnotes themselves separately at the end of the article.

Artwork

Electronic artwork

General points

- Make sure you use uniform lettering and sizing of your original artwork.
- Preferred fonts: Arial (or Helvetica), Times New Roman (or Times), Symbol, Courier.
- Number the illustrations according to their sequence in the text.
- Use a logical naming convention for your artwork files.
- Indicate per figure if it is a single, 1.5 or 2-column fitting image.
- For Word submissions only, you may still provide figures and their captions, and tables within a single file at the revision stage.
- Please note that individual figure files larger than 10 MB must be provided in separate source files.

A detailed [guide on electronic artwork](#) is available.

You are urged to visit this site; some excerpts from the detailed information are given here.

Formats

Regardless of the application used, when your electronic artwork is finalized, please 'save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

EPS (or PDF): Vector drawings. Embed the font or save the text as 'graphics'.

TIFF (or JPG): Color or grayscale photographs (halftones): always use a minimum of 300 dpi.

TIFF (or JPG): Bitmapped line drawings: use a minimum of 1000 dpi.

TIFF (or JPG): Combinations bitmapped line/half-tone (color or grayscale): a minimum of 500 dpi is required.

Please do not:

- Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); the resolution is too low.
- Supply files that are too low in resolution.
- Submit graphics that are disproportionately large for the content.

Color artwork

Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF), or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color online (e.g., ScienceDirect and other sites) regardless of whether or not these illustrations are reproduced in color in the printed version. **For color reproduction in print, you will receive information regarding the costs from Elsevier after receipt of your accepted article.** Please indicate your preference for color: in print or online only. [Further information on the preparation of electronic artwork.](#)

If a figure has been taken from previously copyrighted material, the legend must give full credit to the original source and letters of permission must be submitted with the manuscript. Articles appear in both the print and online versions of the Journal, and wording of the letter should specify permission in both forms of media. Failure to get electronic permission rights may result in the images not appearing in the online version.

Figure captions

Ensure that each illustration has a caption. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Tables. Tables should be self-explanatory and numbered in Roman numerals in the order of their mention in the text. Provide a brief title for each. Type each double-spaced on a separate page. Abbreviations should be defined in a double-spaced footnote at the end of the table. If any material in a table or a table itself has been taken from previously copyrighted material, a double-spaced footnote must give full credit to the original source and permission of the copyright holder must be obtained. Include letters of permission at the time of manuscript submission.

Footnotes that require symbols must use those that are appropriate for the Journal. The accepted symbols, in the order in which they should appear within the table and within the footnotes, are: *, †, ‡, §, ||, ¶, #, **, ††, etc.

Data references

This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. The [dataset] identifier will not appear in your published article.

Reference management software

Most Elsevier journals have their reference template available in many of the most popular reference management software products. These include all products that support [Citation Style Language styles](#), such as [Mendeley](#). Using citation plug-ins from these products, authors only need to select the appropriate journal template when preparing their article, after which citations and bibliographies will be automatically formatted in the journal's style. If no template is yet available for this journal, please follow the format of the sample references and citations as shown in this Guide. If you use reference management software, please ensure that you remove all field codes before submitting the electronic manuscript. [More information on how to remove field codes from different reference management software.](#)

Reference formatting

There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume number/book chapter and the article number or pagination must be present. Use of DOI is highly encouraged. The reference style used by the journal will be applied to the accepted article by Elsevier at the proof stage. Note that missing data will be highlighted at proof stage for the author to correct. If you do wish to format the references yourself they should be arranged according to the following examples:

Reference style

References. The reference list must be numbered serially in the order in which the references appear in the text and typed double-spaced on separate sheets. Reference format should conform to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (Ann Intern Med 1997;126:36-47 or <http://www.icmje.org>). Reference citations to periodicals should include, in the following order: names of the first 3 authors (and et al as necessary to signify any additional authors), title, journal, year, volume, and pages; for example, Hope RR, Scherlag BJ, Lazzara R. Excitation of ischemic myocardium: altered properties of conduction, refractoriness, and excitability. Am Heart J 1980;99:753-65. Journal abbreviations must follow the style used in Cumulated Index Medicus. Book references should include, in the following order: names of the first 3 authors, chapter title, editor(s), book title, volume (if any), edition (if any), city, publisher, year, and inclusive pages of citation (if any); for example, Sherry S. Detection of thrombi. In: Strauss HE, Pitt B, James AE, editors. Cardiovascular nuclear medicine. St. Louis: Mosby; 1974. p. 273-85. Unpublished data and personal communications may be cited in the text but not as references. Authors are responsible for the accuracy of references.

Video

Elsevier accepts video material and animation sequences to support and enhance your scientific research. Authors who have video or animation files that they wish to submit with their article are strongly encouraged to include links to these within the body of the article. This can be done in the same way as a figure or table by referring to the video or animation content and noting in the body text where it should be placed. All submitted files should be properly labeled so that they directly relate to the video file's content. In order to ensure that your video or animation material is directly usable, please provide the file in one of our recommended file formats with a preferred maximum size of 150 MB per file, 1 GB in total. Video and animation files supplied will be published online in the electronic version of your article in Elsevier Web products, including [ScienceDirect](#). Please supply 'stills' with your files: you can choose any frame from the video or animation or make a separate image. These will be used instead of standard icons and will personalize the link to your video data. For more detailed instructions please visit our [video instruction pages](#). Note: since video and animation cannot be embedded in the print version of the journal, please provide text for both the electronic and the print version for the portions of the article that refer to this content.

Data visualization

Include interactive data visualizations in your publication and let your readers interact and engage more closely with your research. Follow the instructions [here](#) to find out about available data visualization options and how to include them with your article.

Research data

This journal encourages and enables you to share data that supports your research publication where appropriate, and enables you to interlink the data with your published articles. Research data refers to the results of observations or experimentation that validate research findings. To facilitate reproducibility and data reuse, this journal also encourages you to share your software, code, models, algorithms, protocols, methods and other useful materials related to the project.

Below are a number of ways in which you can associate data with your article or make a statement about the availability of your data when submitting your manuscript. If you are sharing data in one of these ways, you are encouraged to cite the data in your manuscript and reference list. Please refer to the "References" section for more information about data citation. For more information on depositing, sharing and using research data and other relevant research materials, visit the [research data](#) page.

Data linking

If you have made your research data available in a data repository, you can link your article directly to the dataset. Elsevier collaborates with a number of repositories to link articles on ScienceDirect with relevant repositories, giving readers access to underlying data that gives them a better understanding of the research described.

There are different ways to link your datasets to your article. When available, you can directly link your dataset to your article by providing the relevant information in the submission system. For more information, visit the [database linking page](#).

For [supported data repositories](#) a repository banner will automatically appear next to your published article on ScienceDirect.

In addition, you can link to relevant data or entities through identifiers within the text of your manuscript, using the following format: Database: xxxx (e.g., TAIR: AT1G01020; CCDC: 734053; PDB: 1XFN).

Mendeley Data

This journal supports Mendeley Data, enabling you to deposit any research data (including raw and processed data, video, code, software, algorithms, protocols, and methods) associated with your manuscript in a free-to-use, open access repository. During the submission process, after uploading your manuscript, you will have the opportunity to upload your relevant datasets directly to *Mendeley Data*. The datasets will be listed and directly accessible to readers next to your published article online.

For more information, visit the [Mendeley Data for journals page](#).

Data statement

To foster transparency, we encourage you to state the availability of your data in your submission. This may be a requirement of your funding body or institution. If your data is unavailable to access or unsuitable to post, you will have the opportunity to indicate why during the submission process, for example by stating that the research data is confidential. The statement will appear with your published article on ScienceDirect. For more information, visit the [Data Statement page](#).

AFTER ACCEPTANCE

Online proof correction

To ensure a fast publication process of the article, we kindly ask authors to provide us with their proof corrections within two days. Corresponding authors will receive an e-mail with a link to our online proofing system, allowing annotation and correction of proofs online. The environment is similar to MS Word: in addition to editing text, you can also comment on figures/tables and answer questions from the Copy Editor. Web-based proofing provides a faster and less error-prone process by allowing you to directly type your corrections, eliminating the potential introduction of errors.

If preferred, you can still choose to annotate and upload your edits on the PDF version. All instructions for proofing will be given in the e-mail we send to authors, including alternative methods to the online version and PDF.

We will do everything possible to get your article published quickly and accurately. Please use this proof only for checking the typesetting, editing, completeness and correctness of the text, tables and figures. Significant changes to the article as accepted for publication will only be considered at this stage with permission from the Editor. It is important to ensure that all corrections are sent back to us in one communication. Please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed. Proofreading is solely your responsibility.

Once an article is published online as an Article in Press, no further corrections can be made to the article, except as an erratum or corrigendum, and then only at the Editor's discretion to correct a scientific error.

Reprints. Single reprints must be obtained from the author. Reprint order forms will be sent to authors along with their galley pages.

AUTHOR INQUIRIES

For inquiries relating to the submission of articles (including electronic submission) please visit this journal's homepage (<https://www.journals.elsevier.com/american-heart-journal>). For detailed instructions on the preparation of electronic artwork, please visit <https://www.elsevier.com/artworkinstructions>. Contact details for questions arising after acceptance of an article, especially those relating to proofs, will be provided by the publisher. You can track accepted articles at <https://www.elsevier.com/trackarticle>. You can also check our Author FAQs at <https://www.elsevier.com/authorFAQ> and/or contact our [Support Center](#).