Clinical risk factors for new-onset atrial fibrillation in acute myocardial infarction
A systematic review and meta-analysis.

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Abstract
New-onset atrial fibrillation (NOAF) remains common arrhythmia in acute myocardial infarction (AMI), and is closely associated with increased subsequent cardiovascular mortality. Our meta-analysis aims to summarize more clinical risk factors for NOAF.

Comprehensive systematic search of MEDLINE, EMBASE, and the Cochrane Library were carried out to find relevant studies inception to December 2017. Pooled mean difference (MD) and 95% confidence interval (CI) were calculated to evaluate the value of clinical risk factors in the prediction of NOAF after AMI.

Eleven studies containing 9570 patients were included in the meta-analysis. Overall, older age and increased heart rate (HR) levels had a significant positive association with NOAF in patients with AMI. The MD in age between the patients with, and those without NOAF, was 8.22 units (95% confidence interval [CI]: 7.44–9.01), test for overall effect z score = 20.51 (P < .00001, $I^2 = 0\%$). Moreover, the MD in a subgroup analysis for HR levels between the patients with, and those without NOAF was 4.34 units (95% CI: 2.56–6.11), test for overall effect z score = 4.78 (P < .00001, $I^2 = 31\%$).

In patient with AMI, our meta-analysis demonstrated that older age and increased HR levels on admission are related to greater risk of NOAF.

Abbreviations: AF = atrial fibrillation, AMI = acute myocardial infarction, CI = confidence interval, DBP = diastolic blood pressure, HR = heart rate, MD = mean difference, MeSH = medical subject heading, NOAF = new-onset atrial fibrillation, NOS = Newcastle-Ottawa Scale, SBP = systolic blood pressure, SE = standard error.

Keywords: acute myocardial infarction, age, atrial fibrillation, heart rate

1. Introduction
Acute myocardial infarction (AMI) remains one of the leading causes of death globally. In spite of the widespread use of contemporary therapies, new-onset atrial fibrillation (NOAF) remains common arrhythmia in AMI, and is closely associated with considerable worse prognosis including prolonged hospitalization and all-cause mortality.¹⁻⁵ Therefore, the identification of clinical risk factors related to NOAF in AMI is an important goal. Previous studies have demonstrated several risk factors related to NOAF, such as C-reactive protein, N-terminal pro-brain natriuretic peptide, CHADS2 score, high sensitivity troponin T, left ventricular ejection fraction, left atrium diameter, and obesity among others.⁶⁻¹¹ However, the definite risk stratification of NOAF in AMI remains uncertain, and the aim of our systematic review and meta-analysis is to summarize more clinical risk factors for NOAF. To our knowledge, only a few studies directly evaluated the associations between age or heart rate (HR) and NOAF in patients with AMI. So we conducted this comprehensive meta-analysis to explore the impact of age or HR on NOAF following AMI by collecting data for previously published studies. Besides, the relationship of systolic blood pressure (SBP) or diastolic blood pressure (DBP) and NOAF was also assessed.

2. Methods
2.1. Identification of studies
A comprehensive systematic search of MEDLINE, EMBASE, and the Cochrane Library were carried out to find relevant studies inception to December 2017. The medical subject heading (MeSH) and text words for the term age or HR were combined with the MeSH term atrial fibrillation and AMI. Reference lists from the identified articles were manually examined for relevant new articles. Non-English language articles were not included.

2.2. Selection criteria
Abstracts and titles of related articles were initially scanned by a reviewer. Potentially relevant articles were then considered by at least 2 independent reviewers. Disagreements were resolved by
discussion or upon consensus from a 3rd or 4th reviewer. Two reviewers agreed on the inclusionary or exclusionary status of 90% of the reviewed studies. Full texts of the selected articles were then screened by both authors for inclusion in the review. All disagreements were resolved by consensus. The included studies for analyses had to meet the following criteria: they were observational studies which include patients with AMI, which was defined as chest pain, elevated creatine kinase-MB or troponin level, and changed electrocardiogram according to guidelines; mean and standard deviation of age were reported; they used NOAF rates as an outcome; they were approved for the investigational review committee on human research. The exclusion criteria were: study included patients with a history of persistent or paroxysmal AF; studies were not published in English; abstracts without the full text.

2.3. Quality assessment and data extraction

Quality assessments were evaluated with the Newcastle-Ottawa Scale (NOS) list for nonrandomized studies. Each included study was in 3 aspects using this "star system": the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest (Supplementary Material, http://links.lww.com/MD/D79).

2.4. Statistical analysis

All analyses were conducted with the use of Review Manager, version 5.3 (Revman, The Cochrane Collaboration; Oxford, UK). The association strength between variable and NOAF was measured by mean difference (MD) and 95% confidence interval (CI). The significance of pooled MD was tested by z test \( (P < .05 \) was considered significant). Heterogeneity was evaluated with Cochran Q statistic and quality by \( I^2 \) statistic. We premeditated that mild heterogeneity might be <30% percent of the variability in point estimates and the values of \( I^2 \) exceeding 50% might be expressed as significant heterogeneity, so we considered to use the random-effects model for study, if not, use a fixed-effects model. Publication bias was also evaluated by inspecting funnel plots.

3. Results

3.1. Study Characteristics

From the initial 1690 studies, 11 were included in the meta-analysis (Fig. 1).\[7,8,10,12–19\] As a result, 9570 patients were involved in our analysis: 804 patients in AF group and 8766 patients in without AF group. The NOS for assessing the quality of the 11 studies is shown in Table 1 and the scores ranged from 6 to 8. Table 1 presents the characteristics of each study. The mean age of patients in the included studies ranged from 58 to 79 years and the rate of NOAF ranged from 4.8% to 20.7%.

3.2. Quantitative data synthesis

Overall, there was a significant positive association between age or HR and NOAF in patient with AMI. As shown in Figure 2, the

![Figure 1](image_url)
MD in age between the patients with, and those without NOAF was 8.22 units (95% CI: 7.44–9.01), test for overall effect $z$ score = 20.51 ($P < .00001$, $I^2 = 0\%$). However, an asymmetric funnel plot shows the possible existence of publication bias (Fig. 3). Because of the small sample size, we cannot explain the exact cause of heterogeneity in our meta-analysis.

Moreover, the MD in a subgroup analysis for HR levels between the patients with, and those without NOAF was 4.34 units (95% CI: 2.56–6.11), test for overall effect $z$ score = 4.78 ($P < .00001$, $I^2 = 31\%$) (Fig. 4). Besides, the MD in a subgroup analysis for SBP levels between the patients with, and those without NOAF was 0.72 units (95% CI: −3.57 to 1.16), test for overall effect $z$ score = 1.00 ($P = 0.32$, $I^2 = 0\%$) (Fig. 5B).

### 4. Discussion

Present meta-analysis demonstrated that patients who were older were associated with NOAF occurrence after AMI, and also found that increased HR levels on admission were related to greater risk of NOAF following AMI. Furthermore, we also report that there was no relation to blood pressure on admission and NOAF in AMI. Thus, our results may have important clinical implications with adding age and HR into the evaluation tools for risk stratification of NOAF in AMI.

There is no doubt that NOAF gives rise to worse outcomes in AMI patients.\(^1\)\(^–\)\(^5\) Hence, it is important to understand the risk stratification of NOAF clearly. However, although plenty of studies have attempted to determine predictors for the occurrence of NOAF in the setting of AMI, the exact mechanisms remain unclear. For previous studies,\(^6\)\(^–\)\(^13,17,18\) risk factors for the development of new-onset AF included age, female sex, obesity, Killip class or heart failure, CHADS2 score, creatinine kinase, C-reactive protein, N-terminal pro-brain natriuretic peptide, levels of left ventricular ejection fraction and left atrium diameter.

To the best of our knowledge, present meta-analysis is the first study to directly assess the impact of age and HR on NOAF in patients with AMI.

In summary, our meta-analysis demonstrates that older and increased HR levels on admission are related to greater risk of NOAF following AMI. As well known, advanced age is associated with greater prevalence and severity of coronary artery disease and higher risk of ischemic complications and mortality.\(^20,21\) Older patients often carried more co-morbidities,
so it was not difficult to understand that old age was a major predisposing factor for the development of AF. HR is an easily and ubiquitously collected vital sign at every clinical patient encounter, and is associated with increased cardiovascular risk in the general population. Evidence also showed that admission HR values could independently predict mortality in patients with AMI. Benjamin et al have demonstrated that increasing HR >65 bpm was associated with worse outcomes, including all-cause and cause-specific mortality, as well as adverse cardiovascular events in patients with AF. HR variability is controlled by a balance between sympathetic and parasympathetic systems, and persistently high resting HRs are seen in stressful situations, chronic illness, and physical inactivity. Several studies indicated that rate control was conducive to reduce cardiovascular morbidity and mortality; rate control has therefore been adopted as the front-line therapy in many patients with AF. Moreover, beyond our expectation, this meta-analysis found that admission SBP and DBP were not associated with NOAF in AMI. However, because of the small sample size, the result of blood pressure and NOAF in our analysis should be interpreted cautiously.

Several potential limitations of the present meta-analysis should be mentioned. First, although we have collected all the eligible studies, the sample size of the included studies was not large enough. Second, our analysis was based on observational studies, which may result in increasing the potential biases of such studies. Third, present meta-analysis did not include cutoff values about age or HR because the included studies did not have cutoff value data to use. Finally, all included studies were not directly evaluating the relations of age or HR and NOAF, so the potential confounders might have not entirely eliminated.

5. Conclusions
In conclusion, our meta-analysis demonstrated that older age and increased HR levels on admission are related to greater risk of
NOAF following AMI, and there were no relation of blood pressure and NOAF in AMI.

**Author contributions**

Data curation: Jing He.

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**References**

[1] Nattel S. New ideas about atrial fibrillation 50 years on. Nature 2002;415:519–26.

[2] Pai SM, Pai RG. Management of atrial fibrillation. N Engl J Med 1992;327:1031.

[3] Jabre P, Jouven X, Adnet F, et al. Atrial fibrillation and death after myocardial infarction: a community study. Circulation 2011;123:2094–100.

[4] Rathore SS, Berger AK, Weinfurt KP, et al. Acute myocardial infarction complicated by atrial fibrillation in the elderly: prevalence and outcomes. Circulation 2000;101:969–74.

[5] Asanin M, Perunicic J, Mrdovic I, et al. Prognostic significance of new atrial fibrillation and its relation to heart failure following acute myocardial infarction. Eur J Heart Fail 2005;7:671–6.

[6] Zeng RX, Chen MS, Lian BT, et al. Left ventricular ejection fraction and left atrium diameter related to new-onset atrial fibrillation following acute myocardial infarction: a systematic review and meta-analysis. Oncotarget 2017;8:1137–44.

[7] Aronson D, Boulos M, Suleiman A, et al. Relation of C-reactive protein and new-onset atrial fibrillation in patients with acute myocardial infarction. Am J Cardiol 2007;100:733–7.

[8] Bahouth F, Muttalld, Hammersma H, et al. Left ventricular diastolic dysfunction predicts new-onset atrial fibrillation after acute myocardial infarction. Eur Heart J 2010;31:865.

[9] Parashar S, Langberg JJ, Vaccarino V, et al. Elevated BNP predicts new-onset atrial fibrillation complicating acute myocardial infarction: Analysis of the triumph registry. Journal of the American College of Cardiology 2010;55: A7:E61.

[10] Parashar S, Kella D, Reid KJ, et al. New-onset atrial fibrillation after acute myocardial infarction and its relation to admission biomarkers (from the TRIUMPH registry). Am J Cardiol 2013;112:1390–5.

[11] Guarnaccia C, Stamboul K, Garnier F, et al. Obesity and new-onset atrial fibrillation in acute myocardial infarction: a gender specific risk factor. Int J cardiol 2014;176:1039–41.

[12] Aronson D, Mutlak D, Bahouth F, et al. Restrictive left ventricular filling pattern and risk of new-onset atrial fibrillation after acute myocardial infarction. Am J Cardiol 2011;107:1738–43.

[13] Gu P, Parlak E, Schellings DA, et al. Association of serial high sensitivity troponin T with onset of atrial fibrillation in STElevation myocardial infarction patients undergoing primary percutaneous coronary intervention. Eur Heart J Acute Cardiovasc Care 2016;33:42–3.

[14] Cicek D, Camsari A, Pekdemir H, et al. Predictive value of P-wave signal-averaged electrocardiogram for atrial fibrillation in acute myocardial infarction. Ann Noninvasive Electrocardiol 2003;8:233–7.

[15] Gedikli O, Orem C, Baykan M, et al. Association between serum C-reactive protein elevation and atrial fibrillation after first anterior myocardial infarction. Clin Cardiol 2008;31:492–7.

[16] Yoshizaki T, Umetani K, Ino Y, et al. Activated inflammation is related to the incidence of atrial fibrillation in patients with acute myocardial infarction. Intern Med 2012;51:1467–71.

[17] Dorje T, Wang X, Shao M, et al. Plasma N-terminal pro-brain natriuretic peptide levels predict new-onset atrial fibrillation in patients with acute myocardial infarction. Int J Cardiol 2013;168:3135–7.

[18] Zhang X, Li G, Zhao Z, et al. The value of CHADS2 score in predicting new-onset atrial fibrillation in Chinese patients with acute myocardial infarction. Int J Cardiol 2014;176:135–7.

[19] Hwang HJ, Ha JW, Joung B, et al. Relation of inflammation and left atrial remodeling in atrial fibrillation occurring in early phase of acute myocardial infarction. Int J Cardiol 2011;146:28–31.

[20] Li S, Barywani S, Fu M. Impact of heart rate in atrial fibrillation versus sinus rhythm on mortality in octogenarian patients with acute coronary syndrome. Pan Afr Med J 2017;28:89.

[21] Kolloch R, Legler UF, Champoon A, et al. Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: findings from the INternational VErapamil-SR/trandolapril (INVEST). Eur Heart J 2008;29:1327–34.

[22] Prasada S, Oswalt C, Yehosh P, et al. Heart rate is an independent predictor of all-cause mortality in individuals with type 2 diabetes: the diabetes heart study. World J Diabetes 2018;9:33–9.

[23] Honda T, Kanazawa H, Koga H, et al. Heart rate on admission is an independent risk factor for poor cardiac function and in-hospital death after acute myocardial infarction. J Cardiol 2010;56:197–203.

[24] Zhang D, Shen X, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. CMAJ 2016;188:E53–63.
[25] Legaai C, Jouven X, Tafflet M, et al. Resting heart rate, mortality and future coronary heart disease in the elderly: the 3C Study. Eur J Cardiovasc Prev Rehabil 2011;18:488–97.
[26] Hartaigh B, Allore HG, Trentalange M, et al. Elevations in time-varying resting heart rate predict subsequent all-cause mortality in older adults. Eur J Prev Cardiol 2015;22:527–34.
[27] Custodis F, Roggenbuck U, Lehmann N, et al. Resting heart rate is an independent predictor of all-cause mortality in the middle aged general population. Clin Res Cardiol 2016;105:601–12.
[28] Palatini P, Julius S. Elevated heart rate: a major risk factor for cardiovascular disease. Clin Exp Hypertens 2004;26:637–44.
[29] Johansen CD, Olsen RH, Pedersen LR, et al. Resting, night-time, and 24h heart rate as markers of cardiovascular risk in middle-aged and elderly men and women with no apparent heart disease. Eur Heart J 2013;34:1732–9.
[30] Han Z, Yan-min Y, Jun Z, et al. Prognostic value of admission heart rate in patients with ST-segment elevation myocardial infarction: role of type 2 diabetes mellitus. BMC Cardiovasc Disord 2012;12:104.
[31] Davidovic G, Iric-Cupic V, Milanov S. Associated influence of hypertension and heart rate greater than 80 beats per minute on mortality rate in patients with anterior wall STEMI. Int J Clin Exp Med 2013;6:358–66.
[32] Davidovic G, Iric-Cupic V, Milanov S, et al. When heart goes “BOOM” to fast. Heart rate greater than 80 as mortality predictor in acute myocardial infarction. Am J Cardiovase Dis 2013;3:120–8.
[33] Steinberg BA, Kim S, Thomas L, et al. Increased heart rate is associated with higher mortality in patients with atrial fibrillation (AF): results from the outcomes registry for better informed treatment of AF (ORBIT-AF). J Am Heart Assoc 2015;4:e002031.
[34] Korecha D, Holmes J, Krum H, et al. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet 2014;384:2235–43.
[35] Caldentey G, Khairy P, Roy D, et al. Prognostic value of the physical examination in patients with heart failure and atrial fibrillation: insights from the AF-CHF trial (atrial fibrillation and chronic heart failure). JACC Heart Fail 2014;2:15–23.
[36] Hest EK, Mansour M, Ruskin JN. Rate control in atrial fibrillation: targets, methods, resynchronization considerations. Circulation 2011;124:2746–55.