ESC European Society of Cardiology

European Journal of Preventive Cardiology (2025) **00**, 1–11
https://doi.org/10.1093/eurjpc/zwaf492

FULL RESEARCH PAPER
Cardiovascular disease

Chronotropic incompetence during exercise or pharmacological stress is associated with reduced survival in patients with chronic coronary syndromes

Lauro Cortigiani [1]*, Quirino Ciampi[2], Angela Zagatina [3], Elena Kalinina[3], Ratnasari Padang [4], Garvan C. Kane[4], Hector R. Villarraga[4], Adelaide M. Arruda-Olson[4], Nicola Gaibazzi [5], Davide Donelli [5], Rosina Arbucci[6], Jelena Celutkiene[7], Karina Wierzbowska-Drabik[8], Alla Boshchenko[9], Olga Zhuravleva[9], Natalia Sviazova[9], Miguel Amor[10], Maciej Haberka[11], Jaroslaw D. Kasprzak[12], Hugo Rodriguez-Zanella [13], Albert Varga[14], Elisa Merli[15], Jesus Peteiro Vazquez[16], Fausto Rigo[17], Ana Djordjevic-Dikic[18], Ariel Saad[19], Jorge Lowenstein[6], Diego M. Lowenstein Haber[6], Francesco Bovenzi[1], Ylenia Bartolacelli[20], Giovanni L. Tripepi[21], Mauro Pepi [22], Scipione Carerj[23], Patricia A. Pellikka[4], and Eugenio Picano[18] on behalf of the Stress Echo 2030 Study Group

[1]Cardiology Department, San Luca Hospital, via Gulielmo Lippi Francesconi, 55100 Lucca, Italy; [2]Division of Cardiology, Fatebenefratelli Hospital, Benevento, Italy; [3]Cardiosurgery Department, St. Petersburg State University Hospital, St. Petersburg, Russian Federation; [4]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA; [5]University of Parma, Cardiology Department, Parma, Italy; [6]Cardiodiagnosticos, Investigaciones Medicas and Bioimagenes Medical Center, Buenos Aires, Argentina; [7]Centre of Cardiology and Angiology, Clinic of Cardiac and Vascular Diseases, Faculty of Medicine, Institute of Clinical Medicine, Vilnius University, State Research Institute Center for Innovative Medicine Vilnius LT-03101, Lithuania; [8]Department of Internal Diseases and Clinical Pharmacology, Bieganski Hospital, Medical University, Lodz, Poland; [9]Cardiology Research Institute, Tomsk National Research Medical Centre of the Russian Academy of Sciences, Tomsk, Russian Federation; [10]Hospital Echocardiography Laboratory, Ramos Mejia Hospital, Buenos Aires, Argentina; [11]University of Silesia, Cardiology Department, Katowice, Poland; [12]Department of Cardiology, Bieganski Hospital, Medical University, Lodz, Poland; [13]Department of Cardiology, Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico; [14]Institute of Family Medicine, University of Szeged, Szeged, Hungary; [15]Cardiology Unit, Ospedale per gli Infermi, Faenza, Italy; [16]Department of Cardiology, CHUAC- Complexo Hospitalario Universitario A Coruna- University of A Coruna, La Coruna, Spain; [17]Department of Cardiology, Villa Salus Foundation/IRCCS San Camillo Hospital, Venice Venezia, Italy; [18]Cardiology Clinic, University Center Serbia, Medical School, University Clinical Center Serbia, University of Belgrade, Belgrade, Serbia; [19]División de Cardiología, Hospital de Clínicas José de San Martín, Buenos Aires, Argentina; [20]Paediatric Cardiology and Adult Congenital Heart Disease Program, Department of Cardio-Thoracic and Vascular Medicine IRCCS Azienda Ospedaliero-Universitaria di Bologna, Policlinico S. Orsola-Malpighi Hospital Bologna 40100, Italy; [21]CNR, Institute of Clinical Physiology, Pisa-Roma-Reggio Calabria, Italy; [22]Centro Cardiologico Monzino, IRCCS, Milano, Italy; and [23]Cardiology Division, University Hospital Policlinico G. Martino, University of Messina, Messina, Italy

Received 22 April 2025; revised 27 May 2025; accepted 12 July 2025; online publish-ahead-of-print 5 September 2025

Aims Chronotropic incompetence (CI) is a biomarker of cardiac autonomic dysfunction. The aim of the study is to assess the risk stratification value of CI during exercise or pharmacological stress echocardiography in patients with chronic coronary syndromes.

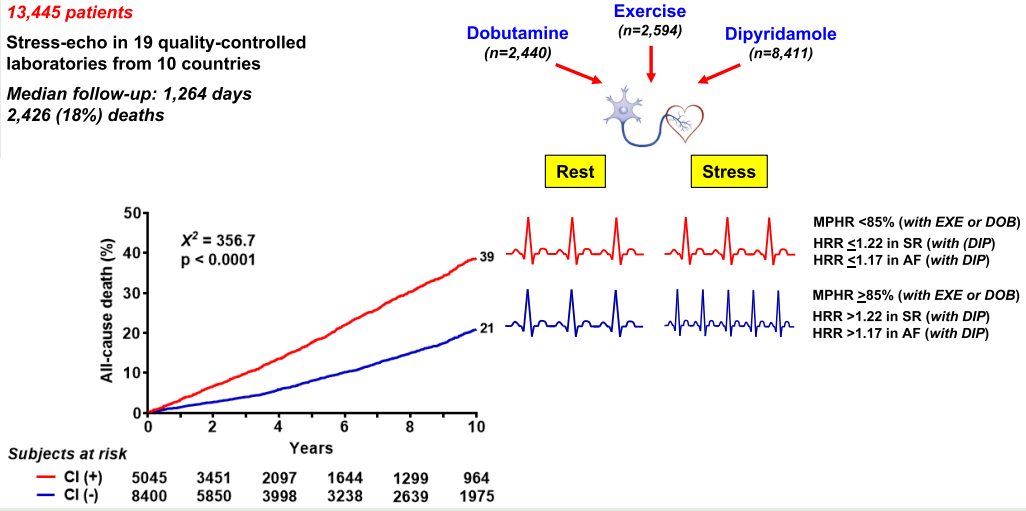
Methods and results In a prospective, multicenter, international, observational study, we enrolled 13 445 patients with known or suspected chronic coronary syndromes who underwent stress echocardiography in 19 clinical sites from 10 countries using either exercise ($n = 2594$), dobutamine ($n = 2440$), or dipyridamole ($n = 8411$). Heart rate was automatically measured from the 1-lead ECG in the echocardiography monitor. We considered CI as failure to reach 85% of the maximal predicted (220-age) heart rate for exercise and dobutamine, and heart rate reserve (peak/rest heart rate) ≤ 1.22 (≤1.17 if in permanent

* Corresponding author. Tel: +390583970953, Email: lacortig@tin.it

atrial fibrillation) for dipyridamole stress. The primary outcome was all-cause death. CI was observed in 5045 patients (38%) and stress-induced regional wall motion abnormalities in 1648 (13%). Over a median follow-up time of 3.4 years (interquartile range, 1.6–9.1 years), there were 2426 (18%) deaths. The 10-year mortality was 39% in patients with and 21% in patients without CI ($P < 0.0001$). CI was associated with a significant increase in 10-year mortality in all age groups ranging from ≤54 years to ≥75 years ($P < 0.0001$). In addition, it was associated with increased mortality ($P < 0.0001$) irrespective of β-blocker use. Cox multivariable analysis revealed that CI was an independent predictor of mortality (HR: 1.60, 95% confidence interval: 1.47–1.74; $P < 0.0001$) together with age, male sex, diabetes mellitus, left ventricular ejection fraction, and resting heart rate.

Conclusion In patients with chronic coronary syndromes, CI during exercise or pharmacological stress is a simple and objective predictor of survival.

Graphical Abstract



Keywords chronotropic incompetence • Heart rate • Echocardiography • Prognosis • Stress

Key points

- In a large international study of over 13 000 patients, those with chronotropic incompetence during stress testing were nearly twice as likely to die within 10 years compared to those without chronotropic incompetence.
- Chronotropic incompetence predicted higher mortality regardless of age, type of stress test, inducible ischaemia during stress, or use of heart medications like β-blockers.

Introduction

Chronotropic incompetence (CI) is broadly defined as the inability of the heart to adequately increase its rate in response to metabolic demands during exercise.[1] Notably, an inadequate chronotropic response can also be elicited by adrenergic pharmacologic stimulation, revealing CI in patients unable to exercise.[2] Whether observed during exercise[3–5] or pharmacological stress,[6,7] CI serves as a marker of reduced cardiac sympathetic reserve and is a predictor of adverse outcomes in patients with chronic coronary syndromes (CCS), heart failure, hypertrophic cardiomyopathy, and various other cardiovascular conditions.[8]

The evaluation of CI is a key component of comprehensive stress echocardiography (SE), offering insights into cardiac autonomic dysfunction. The presence of CI highlights functional and prognostic vulnerabilities, which may add prognostic value to inducible ischaemia, as identified through left ventricular (LV) regional wall motion abnormality (RWMA).[9]

We hypothesized that CI is associated with poorer patient outcomes, regardless of the type of stress used and the presence of stress-induced RWMA. To test this hypothesis, we retrospectively analysed prospectively collected data from a multicenter trial network initiated in 1990. This network has been periodically updated to reflect advancements in techniques and is currently ongoing as part of the Stress Echo 2030 study. Our study evaluated the prognostic significance of CI in patients undergoing SE utilizing various methods of stress, including exercise, dobutamine, and vasodilators, across 19 quality-controlled laboratories in 10 countries.[9] Furthermore, we assessed

the independent and combined prognostic implications of CI and inducible RWMA.

Methods

The study protocol was reviewed and approved by the institutional ethics committees in its latest versions as part of the more comprehensive Stress Echo 2020 study (148-Comitato Etico Lazio-1, 16 July 2016; Clinical trials. Gov Identifier NCT 030.49995) and Stress Echo 2030 study 291/294/295 Comitato Etico Lazio-1, 8 March 2021; Clinical trials. Gov Identifier NCT 050.81115). Written informed consent was obtained from all participants. The complete list of participants in the Stress Echo 2030 study is shown in Supplementary material online, *Table S1*.

Study population

In this retrospective analysis, we initially screened 14 488 patients recruited from August 2001 to February 2024 by 19 certified laboratories in 10 countries (Argentina, Hungary, Italy, Lithuania, Mexico, Poland, Russian Federation, Serbia, Spain, United States). The inclusion criteria were (i) Age >18 years; (ii) referral for known or suspected CCS; (iii) no severe primary valvular or congenital heart disease, no heart transplant recipients, or presence of prognosis-limiting comorbidities, such as advanced cancer, reducing life expectancy to <1 year; (iv) transthoracic echocardiography (TTE) of acceptable quality at rest; (v) willingness to give their written informed consent allowing scientific utilization of observational data, respectful of privacy rights.

Exclusion criteria were poor imaging quality ($n = 178$), refusal to participate in research ($n = 57$), paced rhythm unless programmed in non-rate-adaptive mode during stress testing to allow evaluation of the native sinus node response ($n = 185$), stress-induced arrhythmias or any other cause necessitating premature termination of the test ($n = 343$), and unavailable follow-up information ($n = 280$). The final study population included 13 445 patients (age, 66 ± 11 years; 8128 males, 61%) with CCS referred for SE in 19 accredited laboratories and with follow-up information (*Figure 1*). All patients underwent SE as part of a clinically driven evaluation, according to the referring physician's discretion.

Rest and stress TTE

We used commercially available state-of-the-art ultrasound machines. All patients underwent comprehensive TTE at rest. Certified cardiologists interpreted all measurements according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[10] We assessed the semi-quantitative wall motion score index (WMSI) on a 4-point score ranging from 1 (normal) to 4 (dyskinetic) in an LV 17-segment model.[11–13] In a subset with more recent enrolment (2016 onwards) with the ABCDE protocol, we also measured B-lines (4-site simplified scan), LV contractile reserve as the peak/rest ratio of force (systolic blood pressure/end-systolic volume), and coronary flow velocity reserve (CFVR) measured in the mid-to-distal left anterior descending coronary artery as the stress/rest ratio of the coronary flow peak diastolic velocity.[13] Abnormal result was defined as the stress minus rest B-lines ≥2, LV contractile reserve ≤1.80 when assessed during exercise or dobutamine SE and ≤1.10 when assessed during dipyridamole SE, and CFVR ≤2.0.[13]

Quality control for regional wall motion assessment, B-lines, end-systolic volume, and CFVR assessment was detailed elsewhere.[14] The previously described inter-observer variability was <10% and intra-observer variability

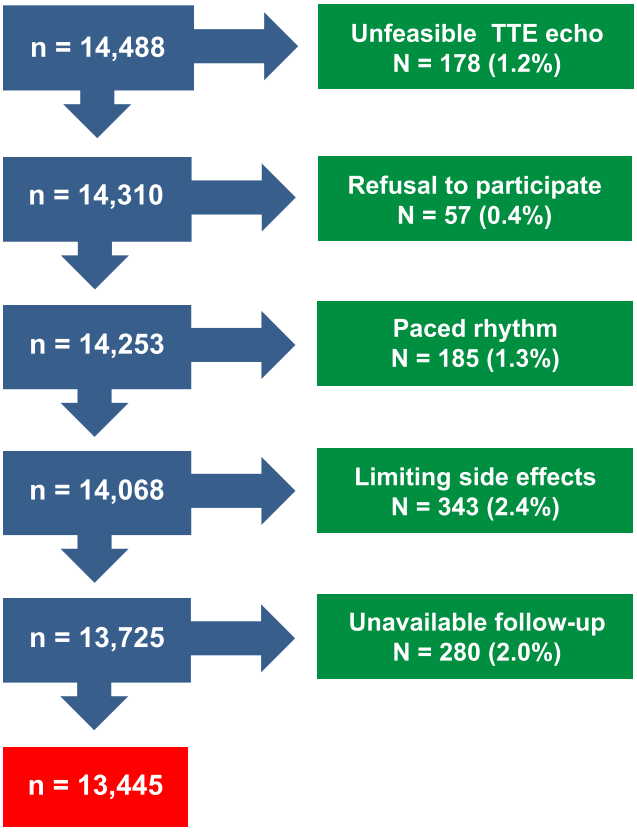


Figure 1 Study flow chart.

was <10% for RWMA, B-lines, and CFVR, and <20% for end-systolic volume.[15]

Based on local expertise and patient characteristics, the employed stress methods were treadmill, semi-supine bike, or upright bike exercise in 2594 patients, dobutamine (from 5 up to 40 μg/kg/min with atropine co-administration up to 1 mg) in 2440 patients, and dipyridamole (0.84 mg/kg in 6 min) in 8411 patients.

Diagnostic endpoints were maximal workload (for exercise) or maximal dose (for drugs), ≥ 85% of target heart rate (for exercise or dobutamine), and development of severe RWMA for all stressors.[13,14]

Chronotropic incompetence

Heart rate was recorded simultaneously with echocardiographic images from the 1-lead electrocardiogram (ECG) displayed in the echocardiography monitor or from the 12-lead ECG recorded every minute during stress. For exercise and dobutamine, the target heart rate was defined as 85% of the maximal predicted (220-age) heart rate (MPHR). For both exercise and dobutamine, we considered CI as the failure to reach 85% of MPHR.[13] For vasodilators, we considered CI as heart rate reserve (HRR, peak/rest heart rate) ≤ 1.22 for patients in sinus rhythm, ≤ 1.17 for those in atrial fibrillation).[13] The previously described inter-observer and intra-observer variability was <1%.[15]

Coronary angiography

Invasive coronary angiography or non-invasive multidetector coronary angiography was available in 2338 patients. Coronary angiography was decided by the referring physician based on symptoms, individual clinical characteristics, and non-invasive imaging results. Obstructive significant coronary artery disease (CAD) was defined by a quantitatively assessed coronary diameter reduction ≥ 50% in the view showing the most severe stenosis. Images were read by experienced invasive cardiologists unaware of the results of SE

Data storage and analysis

The results for each test were entered in the data bank at the time of testing by each accredited recruiting centre and sent monthly to the coordinating institution of Società Italiana di Ecocardiografia e Cardiovascular Imaging, with the electronic case report form with clinical data. Starting in March 2021, data were directly entered by centres in a dedicated RedCap programme in the framework of the SE 2030 study.

Outcome data

All-cause mortality was the only endpoint. This is to avoid misclassification of the cause of death. Deaths were identified from the National Health Service database. Data were collected from each centre by observers unaware of the study hypothesis. Coronary artery bypass surgery (CABG) and percutaneous coronary intervention (PCI) were also registered; however, follow-up was not censored at the time of revascularization.

Statistical analysis

Continuous variables were summarized as mean ± SD, while categorical variables were expressed as absolute numbers and percentages. Comparisons between two groups were performed using independent *t*-tests or χ^2 tests, as appropriate. For comparisons among three or more groups, ANOVA or χ^2 tests were applied. Mortality rates were estimated using Kaplan–Meier curves and compared using the log-rank test. Predictors of incident outcomes were identified through univariable and multivariable Cox regression analyses. Variables significantly associated with the study endpoints in univariable analyses ($P < 0.10$) were included in multivariable Cox models. A stepwise approach was used to identify independent predictors. To determine whether β-blocker use modifies the effect of chronotropic incompetence, the Cox models included a formal CI × β-blocker interaction term.

To compare the model fit improvement, clinical, echocardiographic, and electrocardiographic variables were sequentially introduced into four additive models. The global χ^2 statistic was calculated after the addition of each variable step, with significant increases indicating improved model fit. Multicollinearity was evaluated using correlation matrices, and proportional hazards assumptions were tested using Schoenfeld residuals. When necessary, piecewise Cox regression analyses were conducted to confirm the robustness of findings. Statistical significance was set at $P < 0.05$. Any pairwise or post-hoc tests included appropriate Type-I error correction with the Bonferroni test. Additional sensitivity analyses were performed among patients with coronary angiography data, stratified by stress modality, inducible RWMA, or rhythm. All analyses were two-sided and performed using RStudio (version 2023.06) and SPSS for Windows, release 20.0 (IBM).

Results

An overall population of 13 445 patients was enrolled. CI was present in 5045 (38%) patients. The demographic, clinical, and SE characteristics of patients with and without CI are shown in *Table 1*.

CI was more prevalent during exercise (1409/2594; 54%) compared to dobutamine (873/2440; 36%) or dipyridamole (2763/8411; 33%) stress ($P < 0.0001$).

Compared to patients without CI, those with CI showed a higher prevalence of inducible RWMA, stress–rest B-lines ≥2, reduced CFVR of the left anterior descending coronary artery, and abnormal LV contractile reserve (*Table 1*). In the subset of 2338 patients with coronary angiographic information within 3 months of testing, patients with CI showed a higher prevalence of multivessel CAD (*Table 1*).

CI was slightly more frequent in patients on compared to patients off beta-blockers (47% vs. 35%, $P < 0.001$, see *Table 1*) but the prognostic value was comparable in the two subsets (see *Figures 2* and *3*).

At multivariable logistic regression analysis age, diabetes mellitus, systemic hypertension, previous myocardial infarction, previous CABG, LV ejection fraction, β-blocker therapy at the time of test, and high resting heart rate predicted the presence of CI (*Table 2*).

Outcome data

During a median follow-up of 3.4 years (interquartile range, 1.6–9.1 years), 2426 (18%) deaths occurred. In addition, 1710 (13%) patients underwent coronary revascularization (462 CABG, 1248 PCI) and were not censored; this included 682 of 1648 (41%) with and 1028 of 11 797 (9%) without inducible RWMA ($P < 0.0001$). Considering the group with inducible RWMA, revascularized patients had greater Δ-WMSI than those maintained on medical therapy (0.39 ± 0.25 vs. 0.32 ± 0.25; $P < 0.0001$).

The 10-year mortality was lower in patients investigated with exercise (11%) as compared to those investigated with dobutamine (29%) or dipyridamole (28%). The χ^2 *P*-value for the overall 3-group comparison was $\chi^2 = 459$, $P < 0.0001$.

Mortality at 10 years was nearly 2-fold higher in patients with CI compared to those without CI (39% vs. 21%; $P < 0.0001$) (*Figure 2*). CI was associated with a markedly increased mortality ($P < 0.0001$) irrespective of background β-blocker therapy (*Figure 2*). In addition, it was associated with a significantly greater 10-year mortality in each age group including patients aged ≤54 years (15% vs. 7%; $P < 0.0001$), patients aged 55 to 64 years (24% vs. 11%; $P < 0.0001$), patients aged 65 to 74 years (38% vs. 22%; $P < 0.0001$), and patients aged ≥75 years (60% vs. 45%; $P < 0.0001$).

The annual mortality in patients with and without CI was, respectively, 1.9% and 0.7% ($P < 0.0001$) in those undergoing exercise, 4.6% and

Table 1 Clinical, functional, and angiographic correlates of chronotropic incompetence during stress

	All patients (*n* = 13 445)	Patients with CI (*n* = 5045)	Patients without CI (*n* = 8400)	*P*-value
Age (years)	66 ± 11	67 ± 11	65 ± 11	<0.0001
Males	8128 (61%)	3088 (61%)	5040 (60%)	0.17
Clinical history				
Diabetes mellitus	3499 (26%)	1414 (28%)	2085 (25%)	<0.0001
Arterial hypertension	8893 (66%)	3563 (71%)	5330 (64%)	<0.0001
Hypercholesterolemia	7633 (57%)	2999 (59%)	4634 (55%)	<0.0001
Prior myocardial infarction	3467 (26%)	1559 (31%)	1908 (23%)	<0.0001
Prior PCI	3409 (25%)	1327 (26%)	2082 (25%)	0.05
Prior CABG	1023 (8%)	491 (10%)	532 (6%)	<0.0001
Known CAD	5302 (39%)	2204 (44%)	3098 (37%)	0.009
Ongoing β-blocker therapy	5323 (40%)	2360 (47%)	2963 (35%)	<0.0001
Type of stress				
Exercise	2594 (19%)	1409 (28%)	1185 (14%)	<0.0001
Dobutamine	2440 (18%)	873 (17%)	1567 (19%)	0.05
Dipyridamole	8411 (63%)	2763 (55%)	5648 (67%)	<0.0001
Echocardiographic and hemodynamic parameters at rest				
LV ejection fraction (%)	57 ± 10	56 ± 12	58 ± 9	<0.0001
WMSI	1.17 ± 0.35	1.24 ± 0.42	1.13 ± 0.30	<0.0001
Heart rate (beats/min)	69 ± 12	71 ± 12	68 ± 12	<0.0001
SBP (mmHg)	135 ± 19	135 ± 18	135 ± 20	0.96
DBP (mmHg)	79 ± 17	78 ± 15	80 ± 18	0.08
B-Lines ≥2	828/5127 (16%)	409/2019 (20%)	419/3108 (13%)	<0.0001
Echocardiographic and hemodynamic parameters during stress				
Inducible RWMA	1648 (13%)	938 (19%)	740 (9%)	<0.0001
WMSI	1.19 ± 0.35	1.29 ± 0.42	1.14 ± 0.29	<0.0001
Δ-WMSI (stress–rest)	0.02 ± 0.18	0.05 ± 0.23	0.01 ± 0.15	<0.0001
Heart rate (beats/min)	103 ± 26	96 ± 22	108 ± 26	<0.0001
SBP (mmHg)	145 ± 31	146 ± 32	144 ± 30	0.001
DBP (mmHg)	79 ± 17	78 ± 17	79 ± 17	<0.0001
CFVR of the LAD	7883 (59%)	2686 (53%)	5197 (47%)	<0.0001
CFVR of the LAD ≤2.0	2494/7883 (32%)	1299/2686 (48%)	1195/5197 (23%)	<0.0001
LV Contractile reserve	7709 (57%)	2787 (55%)	4922 (59%)	0.0001
Abnormal LV contractile reserve (≤1.80 when assessed during exercise or dobutamine and ≤1.10 when assessed during dipyridamole stress)	2751/7709 (36%)	1330/2787 (48%)	1421/4922 (29%)	<0.0001
B-Lines	5127 (38%)	2019 (40%)	3108 (37%)	0.0005
Stress–rest B-lines ≥2	1018/5127 (20%)	532/2019 (26%)	486/3108 (16%)	<0.0001
Angiographic findings				
Coronary angiography	2338 (17%)	1093 (22%)	1245 (15%)	<0.0001
No CAD	478/2338 (20%)	221/1093 (20%)	257/1245 (21%)	0.80
1-Vessel disease	945/2338 (40%)	394/1093 (36%)	551/1245 (44%)	<0.0001
Multivessel disease	915/2338 (39%)	478/1093 (44%)	437/1245 (35%)	<0.0001

Data presented are mean value ± SD or number (%) of patients.
CI, chronotropic incompetence; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CAD, coronary artery disease; LV, left ventricular; WMSI, wall motion score index; SBP, systolic blood pressure; DBP, diastolic blood pressure; RWMA, regional wall motion abnormality; CFVR, coronary flow velocity reserve; LAD, left anterior descending; LV, left ventricular,

3.3% ($P = 0.0002$) in those undergoing dobutamine, and 5.4% and 2.2% ($P < 0.0001$) in those undergoing dipyridamole (Bonferroni corrected P values ranging from <0.0001 to 0.0006).

Univariable and multivariable predictors of mortality are reported in *Table 3*. CI showed independent prognostic value with age, male sex, diabetes mellitus, resting LV ejection fraction, and resting heart rate. No effect modification by β-blockers was found on the relationship between chronotropic incompetence and death. In fact, the hazard ratio of chronotropic incompetence for mortality was similar ($P = 0.69$) in patients on (hazard ratio, 2.16; 95% confidence interval, 1.89–2.46; $P < 0.0001$) and in those off β-blocker therapy (hazard ratio, 2.07; 95% confidence interval, 1.87–2.29; $P < 0.0001$).

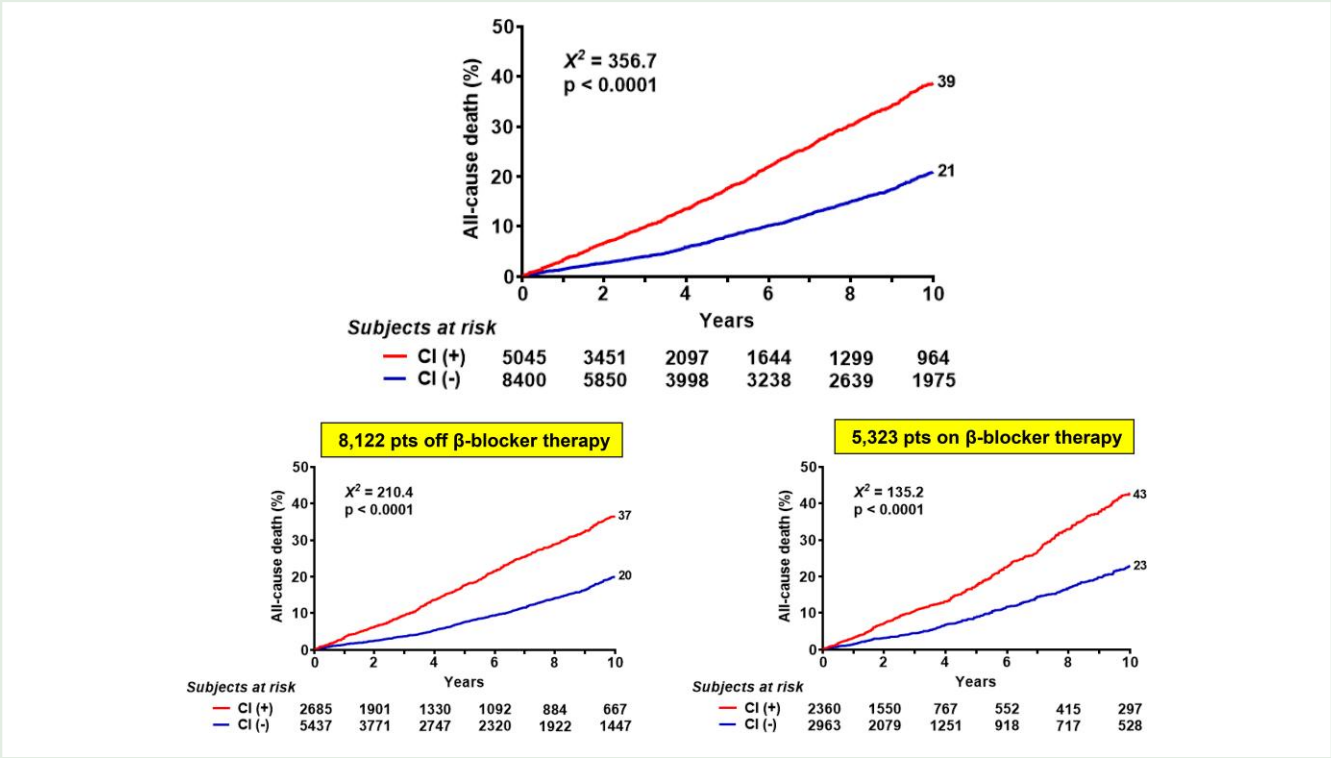


Figure 2 Kaplan–Meier survival curves. At the top of the figure is shown the death rate according to the presence (CI+) or absence (CI-) of CI in the entire study population. At the bottom of the figure is shown the death rate according to the normal (CI-) and abnormal (CI+) chronotropic response in patients studied off (left panel) and on (right panel) β-blocker therapy. CI indicates either a reduction in MPHR (for exercise or dobutamine) or a blunted HRR (for vasodilators). MPHR, maximal predicted heart rate.

The multivariable Cox regression analysis identified independent predictors of mortality across a series of models of increasing complexity (*Figure 3*). The clinical model included age, sex, diabetes mellitus, hypertension, prior CABG, prior myocardial infarction, β-blocker use, and resting heart rate. Age (hazard ratio, 1.08; 95% confidence intervals, 1.08–1.09; $P < 0.0001$), male sex (hazard ratio, 1.43; 95% confidence intervals, 1.35–1.56; $P < 0.0001$), diabetes mellitus (hazard ratio 1.42, 95% confidence intervals 1.30–1.54; $P < 0.0001$), prior CABG (hazard ratio, 1.23; 95% confidence intervals, 1.08–1.39; $P = 0.001$), prior myocardial infarction (hazard ratio, 1.37; 95% confidence intervals, 1.26–1.49; $P < 0.0001$), and resting heart rate (hazard ratio, 1.01; 95% confidence intervals, 1.01–1.02; $P < 0.0001$) were positively associated with mortality (*Figure 3*). Adding LV ejection fraction to the model significantly improved predictive performance, with LV ejection fraction (hazard ratio, 0.96; 95% confidence intervals, 0.96–0.97; $P < 0.0001$) emerging as an independent and inverse predictor. Age, male sex, diabetes mellitus, prior CABG, prior myocardial infarction, and resting heart rate remained significant (*Figure 3*). Introducing Δ-WMSI (hazard ratio, 1.58; 95% confidence intervals, 1.17–2.15; $P = 0.003$) into the model further enhanced prognostic capability (*Figure 3*). Finally, the model incorporating CI demonstrated the strongest discriminatory power. CI (hazard ratio, 1.60; 95% confidence intervals, 1.47–1.74; $P < 0.0001$) was a highly robust predictor, with tight confidence intervals reflecting its reliability (*Figure 3*). Only age, male sex, diabetes mellitus, and—on the edge of significance—stress–rest changes in WMSI remained significant, with CI by far the strongest predictor. The results in *Figure 3* are also reported in Supplementary material online, *Table S2* of Supplementary material to improve their readability.

We also separately analysed patients with coronary angiography information. In multivariable analysis, CI showed a significant prognostic value in the 478 patients without CAD (hazard ratio, 1.55; 95% confidence intervals, 1.04–2.32; $P = 0.03$), with independent value over inducible RWMA (hazard ratio, 1.30; 95% confidence intervals, 0.71–2.37; $P = 0.39$), and in the 1860 patients with CAD (hazard ratio, 1.63; 95% confidence intervals, 1.35–1.97; $P < 0.0001$), with independent value over inducible RWMA (hazard ratio, 0.86; 95% confidence intervals, 0.72–1.04; $P = 0.13$).

In a separate analysis stratified by stress type, at multivariable analysis CI was significant for exercise ($n = 2,594$; hazard ratio, 3.19; 95% confidence intervals, 1.88–5.43; $P < 0.0001$), dobutamine ($n = 2,440$; hazard ratio, 1.45; 95% confidence intervals, 1.20–1.74; $P < 0.0001$), and vasodilator stress ($n = 8,411$; hazard ratio, 1.71; 95% confidence intervals, 1.55–1.89; $P < 0.0001$).

We also separately analysed patients with and without inducible RWMA. In multivariable analysis, CI showed a significant prognostic value in the 1648 patients with inducible RWMA (hazard ratio, 1.24; 95% confidence intervals, 1.00–1.54; $P = 0.05$), and in the 11 797 patients without inducible RWMA (hazard ratio, 1.70; 95% confidence intervals, 1.55–1.86; $P < 0.0001$).

In an additional analysis stratified by rhythm, at multivariable analysis CI was significant for patients in normal sinus rhythm ($n = 12,940$; hazard ratio, 1.62; 95% confidence intervals, 1.49–1.77; $P < 0.0001$) and in those with permanent atrial fibrillation ($n = 505$; hazard ratio, 1.77; 95% confidence intervals, 1.31–2.41; $P < 0.0001$).

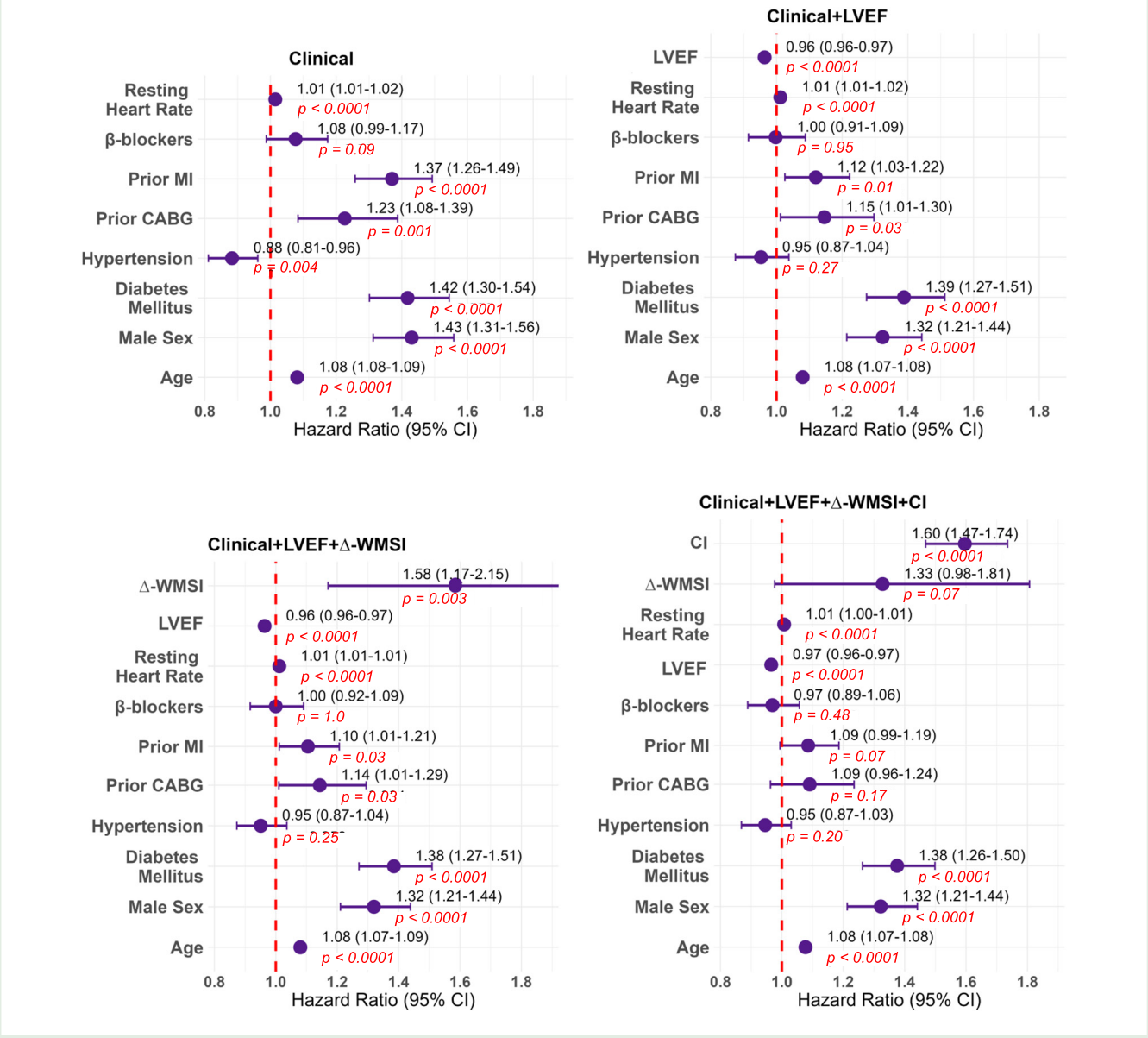


Figure 3 Multivariable predictors of mortality across a series of additive models, including clinical data, LVEF, Δ-WMSI, and CI. The model incorporating CI showed the highest prognostic value CI being a highly robust predictor of mortality. MI, myocardial infarction; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; WMSI, wall motion score index; CI, chronotropic incompetence.

As a *post-hoc* analysis, we limited our analysis to patients ($n = 4881$) studied with exercise or dobutamine stress echocardiography and in normal sinus rhythm, since in these patients heart rate is one of the target endpoints (differently from vasodilator stress) and better fit the definition of CI as the inability of the heart to increase its rate appropriately in response to increased physical activity or metabolic demand. The analysis is presented in the Supplementary material (see Supplementary material online, *Table S3*), showing the value of CI to predict survival also in this more strictly defined subset.

Discussion

In this large population of 13 445 patients with CCS studied with different forms of exercise and pharmacological SE in 19 laboratories of 10 countries, CI was present in 38% of patients. CI was more prevalent with exercise stress than with pharmacologic stress. Risk factors such as diabetes were more prevalent, and values of ejection fraction were lower in the group with CI (see *Table 1*), further emphasizing the potential overlap of factors influencing chronotropic incompetence beyond the classic coronary pathology. The association of chronotropic incompetence with other SE-derived haemodynamic parameters, such as increased B-lines and reduced CFVR, does not necessarily reflect causality and can be considered a marker of the greater functional vulnerability of the patient. Additionally, CI was associated with more extensive CAD, as confirmed by coronary angiography. CI provides valuable functional and prognostic information across all forms of physical and pharmacologic stress testing.

Table 2 Predictors of chronotropic incompetence

	Univariate Logistic Regression		Multivariate Logistic Regression	
Variables	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Age	1.01 (1.01–1.02)	<0.0001	1.01 (1.01–1.02)	<0.0001
Male sex	1.05 (0.98–1.13)	0.17		
Diabetes mellitus	1.18 (1.09–1.28)	<0.0001	1.10 (1.01–1.12)	0.03
Arterial hypertension	1.34 (1.25–1.45)	<0.0001	1.25 (1.15–1.36)	<0.0001
Hypercholesterolemia	1.18 (1.10–1.27)	<0.0001		
Prior myocardial infarction	1.52 (1.41–1.65)	<0.0001	1.30 (1.19–1.42)	<0.0001
Prior CABG	1.54 (1.36–1.75)	< 0.0001	1.25 (1.09–1.43)	0.001
Prior PCI	1.07 (0.99–1.16)	0.11		
LV Ejection fraction	0.98 (0.97–0.98)	<0.0001	0.98 (0.98–0.99)	<0.0001
Ongoing β-blocker therapy	1.61 (1.50–1.73)	<0.0001	1.50 (1.39–1.63)	<0.0001
Resting heart rate	1.02 (1.02–1.02)	<0.0001	1.02 (1.02–1.03)	<0.0001

Abbreviations as in *Table 1*.

Table 3 Univariable and multivariable predictors of mortality

	Univariable analysis		Multivariable analysis	
Variables	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Age, per year	1.08 (1.07–1.08)	<0.0001	1.08 (1.07–1.08)	<0.0001
Male sex	1.16 (1.07–1.26)	<0.0001	1.34 (1.23–1.46)	<0.0001
Diabetes mellitus	1.61 (1.48–1.76)	<0.0001	1.40 (1.29–1.53)	<0.0001
Arterial hypertension	1.14 (1.05–1.24)	0.001		
Hypercholesterolemia	0.90 (0.83–0.97)	0.02		
Prior myocardial infarction	1.48 (1.36–1.60)	<0.0001		
Prior CABG	1.69 (1.50–1.91)	<0.0001		
Prior PCI	0.99 (0.90–1.08)	0.77		
Known CAD	1.53 (1.42–1.66)	<0.0001		
β-Blocker therapy	1.21 (1.12–1.32)	<0.0001		
LV Ejection fraction, per %	0.96 (0.95–0.96)	<0.0001	0.96 (0.96–0.97)	<0.0001
Resting WMSI, per unit	2.97 (2.73–3.25)	<0.0001		
Inducible RWMA	1.15 (1.03–1.29)	0.02		
Peak WMSI, per unit	2.97 (2.71–3.24)	<0.0001		
Δ-WMSI (stress–rest)	1.38 (1.03–1.84)	0.03		
Resting heart rate, per bpm	1.00 (1.00–1.01)	0.001	1.01 (1.00–1.01)	< 0.0001
Chronotropic incompetence	2.15 (1.99–2.33)	<0.0001	1.63 (1.50–1.77)	< 0.0001

BPM, beats per minute. Other abbreviations are as in *Table 1*.

The mechanism of CI

The primary mechanism underlying CI during stress testing is the down-regulation of cardiac β1-adrenergic receptors, characterized by reduced receptor density and sensitivity due to chronically elevated sympathetic drive. A progressive decline in HRR is accompanied by increased cardiac noradrenaline levels, alongside a parallel reduction in tissue noradrenaline, nerve density, and nerve function. Neural remodelling, marked by heightened sympathetic nerve activity and diminished parasympathetic tone, adversely affects survival through mechanisms such as increased susceptibility to atrial and ventricular arrhythmias and excessive sympathetic signalling contributing to cardiac fibrosis.[16]

The mediator of increased sympathetic tone during exercise is cardiac noradrenaline, released by cardiac afferent nerve endings. These afferents relay signals from baroreceptors and the intrinsic cardiac nervous system to the lower brainstem, activating cardiac efferent nerves that project to the sinus node via β1-receptor stimulation. Anatomically, the right stellate ganglion primarily innervates the sinus node, while the left stellate ganglion innervates the atrioventricular node. A similar chronotropic stimulation of the sinus node can be achieved by exogenous catecholamines like dobutamine.[17]

With vasodilator stress, exogenous adenosine or endogenous adenosine (accumulating after dipyridamole infusion) activates cardiac afferent neurons via A2a adenosine receptors. These afferents are

located in the carotid body, skeletal muscle, heart, and kidneys, and function independently of inducible ischaemia or arterial hypotension.[18] The blunted heart rate response in some patients may reflect either heightened baseline adrenergic activity (evidenced by higher resting heart rates) or reduced adrenergic responsiveness - both hallmarks of autonomic dysfunction. Several potential pathways link CI to mortality, such as autonomic dysfunction as a trigger of arrhythmias and sudden death, endothelial dysfunction, and enhanced low-grade systemic inflammation.[18]

Since the definition of CI differs between vasodilator stress and exercise or dobutamine SE, a theoretical and methodological contradiction may appear to exist. However, this contradiction is only apparent for several reasons. First, each type of stress is associated with previously validated cut-off values based on prognostic endpoints. Second, variability in cut-off values is common in functional testing; for example, normal reference values for pulmonary hemodynamics vary with different forms of exercise stress (e.g. supine vs. upright testing). Third, and most importantly, CI retains its prognostic significance—using stress-specific thresholds—across diverse patient populations, including those with and without CAD, under various treatment regimens, with differing cardiac rhythms, and across different stress modalities. This consistency supports the prognostic value of CI as a simple yet powerful clinical marker.

In the present study, confounders such as the heterogeneity of population (with and without previous myocardial infarction and coronary revascularization), risk factors profile (with high prevalence of diabetes and hypertension), different resting rhythm conditions (normal sinus rhythm and chronic atrial fibrillation), variability of concomitant drug therapy (off or on beta-blockers), underlying coronary anatomy (from no CAD to severe CAD), and left ventricular function (from normal to depressed ejection fraction) make a one-fits-all interpretation of mechanisms of CI very challenging.

Comparison with previous studies

The prognostic value of CI has previously been demonstrated to be both independent of and additive to perfusion defects observed during exercise or pharmacologic testing.[4,19–21] When combined with SE, the additive value of CI extends beyond inducible RWMA during exercise,[22,23] dobutamine,[24] and vasodilator stress testing.[25]

The present study confirms and extends these prior findings, offering unique contributions for several reasons. First, it is a multicenter, international, prospective investigation. All-cause mortality was the sole endpoint, ensuring a robust and uniform outcome measure. The study involved 19 certified laboratories across 10 countries, revealing a consistent pattern of CI's prognostic impact across diverse regions and ethnic groups.

The selection criteria were broad, encompassing patients with prior coronary revascularization and those on β-blockers, groups that were excluded from earlier proof-of-concept studies.[23] All patients had measures of LV function, missing in other pioneering exercise studies.[5] Additionally, various stress modalities were employed based on local expertise and test availability. This approach demonstrated that the underlying mechanism of reduced cardiac sympathetic reserve can be effectively unmasked across all exercise and pharmacological stress types.

Study limitations

No core lab reading was employed in the present study, for the sparing of resources and to reproduce the conditions of a real-world study. A central core lab reading would have ensured a more homogeneous and consistent reading, but also a prohibitive cost in economic and human resources. However, upstream quality control was performed before allowing each centre to enter the data bank.[15]

HRR and MPHR can be obtained in all patients, except those with paced rhythm, who were excluded from the analysis. HRR is also obtained in patients with atrial fibrillation since the chronotropic response and the prognostic value of CI are maintained in these patients.[26–28]

CI can be dependent on many variables. There is an age-dependent decline in HRR. Drugs such as β-blockers reduce resting heart rate and reduce the sensitivity and prognostic accuracy of inducible RWMA, but do not affect the prognostic impact of CI.[29] Other drugs, such as non-dihydropyridine calcium-channel blockers or ivabradine, may affect CI.

There is no single universally accepted cut-off for CI, since it can vary with the type of exercise, level of exercise, gender, and age. The majority of studies in the literature have used failure to attain ≥85% of the MPHR, measured during a graded exercise test, as the primary criterion for CI, but others have considered 80% or even 70% as the most appropriate cut-off.[29] The criterion is the same for dobutamine stress, and obviously lower (≤1.22) for vasodilator stress. The simplicity of this criterion made it especially attractive for imaging specialists working in the SE lab, where there are so many things to see and so little time available. Nevertheless, this simple index was previously validated and provided important prognostic information in addition to RWMA in predicting major adverse events in populations referred to stress testing. However, the reliance on the '220—age' formula has known limitations in elderly patients and those on beta-blockers. In addition, the underlying mechanisms of CI (e.g. autonomic dysfunction or beta-adrenergic receptor downregulation) were not explored, and direct mechanistic data are lacking in this cohort.

We focused on HRR and MPHR, both of which are indices of cardiac sympathetic reserve. A similar approach could have been employed to assess heart rate recovery. Typically defined as the decrease in heart rate 1 min after cessation of exercise, heart rate recovery is a well-established predictor of all-cause mortality in coronary artery disease (CAD). It reflects the interplay between parasympathetic reactivation and sympathetic withdrawal. However, it cannot be assessed after pharmacological stress, and its risk stratification value is partially redundant with that of CI.[29]

The outcome endpoint was all-cause death, but in theory, CI should be more predictive of sudden death. The missing data on the exact cause of death did not allow for performing competing risk regression analysis to isolate cardiac vs. non-cardiac death. Nevertheless, all-cause death is the most clinically meaningful endpoint and easier to ascertain than the specific causes of death.

In principle, all antianginal therapy should be withdrawn 48 h before testing to optimize the diagnostic accuracy and information on chronotropic reserve with all forms of testing. In practice, a complete therapy withdrawal can be impractical or even dangerous, depending on the type of patient and type of therapy.[12,13] Our study design did not interfere with local practice and experience, and 40% of patients were studied on beta-blocker therapy, but this did not substantially affect the prognostic impact of CI with all types of stressors.

Inducible RWMA has lost its predictive power in a multivariate model when CI was added. Inducible RWMA is a cornerstone of decision-making and usually triggers invasive examinations and ischaemia-driven interventions, while CI has no standardized therapy currently available and is often not considered by the referring physician in the management of the patient.[30]

Clinical implications

ECG-based assessment of CI is simple, objective, quantitative, independent of imaging, and universally accessible to cardiologists, except in patients with paced rhythms. A blunted heart rate response can be reliably identified during physical or pharmacological stress using automated heart rate readings. The measurement exhibits no inter- or intra-observer variability.

CI is an independent predictor of overall mortality, even after adjustment for inducible RWMA. Consequently, ECG assessment complements SE by providing additional prognostic information. Furthermore, CI serves as a promising biomarker for cardiac autonomic and, potentially, an actionable therapeutic target.[16]

Conclusions

In patients with CCS, CI during exercise or pharmacological SE serves as a simple, inexpensive, quantitative, and objective predictor of survival, independent of ischaemia. Its ability to stratify risk and predict survival is evident across various contexts, including assessment using MPHR with exercise or dobutamine or HRR with vasodilators (*Graphical Abstract*), in patients with and without background β-blocker therapy, and using all stress modalities.

CI shows excellent reproducibility without requiring additional imaging or analysis time. This parameter provides valuable insights into cardiac autonomic, an area not directly assessed by SE based on RWMA. Consequently, it represents both a diagnostic opportunity and a potential therapeutic target.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contribution

L.C., Q.C., P.A.P., and E.P. contributed to the conception or design of the work. L.C., Q.C., A.Z., E.K., R.P., G.C.K., H.V., A.M.A.O., N.G., D.D., R.A., J.C., K.W.D., A.B., O.Z., N.S., M.A., M.H., J.D.K., H.R.Z., K.V., E.M., J.P.V., F.R., A.D.D., A.S., J.L., D.M.L.H., F.B., contributed to the acquisition, analysis, or interpretation of data for the work. G.L.T. was responsible for the statistical plan and data analysis. Y.B. was responsible for database structure, data check, and data extraction. M.P. and S.C. endorsed, disseminated, and partially funded the study as President and past-president of SIECVI. L.C., P.A.P., and E.P. drafted the manuscript. All gave final approval and agreed to be accountable for all aspects of work, ensuring integrity and accuracy.

Funding

Unrestricted funding from Società Italiana di Ecocardiografia e Cardiovascular Imaging (SIECVI).

Conflict of interest: none declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Katritsis D, Camm AJ. Chronotropic incompetence: a proposal for definition and diagnosis. *Br Heart J* 1993;**70**:400–402.
2. White M, Leenen FH. Effects of age on cardiovascular responses to Adrenaline in man. *Br J Clin Pharmacol* 1997;**43**:407–414.
3. Ellestad MH, Wan MK. Predictive implications of stress testing. Follow-up of 2700 subjects after maximum treadmill stress testing. *Circulation* 1975;**51**:363–369.
4. Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. *JAMA* 1999;**281**:524–529.
5. Gulati M, Shaw LJ, Thisted RA, Black HR, Bairey Merz CN, Arnsdorf MF. Heart rate response to exercise stress testing in asymptomatic women: the St. James women take heart project. *Circulation* 2010;**122**:130–137.
6. Hage FG, Iskandrian AE. Heart rate response during vasodilator stress myocardial perfusion imaging: mechanisms and implications. *J Nucl Cardiol* 2010;**17**:536–e539.
7. Elhendy A, van Domburg RT, Bax JJ, Nierop PR, Geleijnse ML, Ibrahim MM, *et al.* The functional significance of chronotropic incompetence during dobutamine stress test. *Heart* 1999;**81**:398–403.
8. Brubaker PH, Kitzman DW. Chronotropic incompetence. Causes, consequences, and management. *Circulation* 2011;**123**:1010–1020.
9. Picano E, Ciampi Q, Arbucci R, Cortigiani L, Zagatina A, Celutkiene J, *et al.* Stress Echo 2030: the new ABCDE protocol defining the future of cardiac imaging. *Eur Heart J Suppl* 2023;**25**:C63–C67.
10. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233–270.
11. Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R, *et al.* The clinical use of SE in non-ischaemic heart disease: recommendations from the European association of cardiovascular imaging and the American society of echocardiography. *Eur Heart J Cardiovasc Imaging* 2016;**17**:1191–1229.
12. Pellikka PA, Arruda-Olson A, Chaudhry FA, Chen MH, Marshall JE, Porter TR, *et al.* Guidelines for performance, interpretation, and application of stress echocardiography in ischemic heart disease: from the American Society of Echocardiography. *J Am Soc Echocardiogr* 2020;**33**:1–41.
13. Picano E, Pierard L, Peteiro J, Djordjevic-Dikic A, Sade LE, Cortigiani L, *et al.* The clinical use of stress echocardiography in chronic coronary syndromes and beyond coronay artery disease: a clinical consensus statement from the European Association of Cardiovascular Imaging of the ESC. *Eur Heart J Cardiovasc Imaging* 2024;**25**:e65–e90.
14. Ciampi Q, Zagatina A, Cortigiani L, Gaibazzi N, Daros CB, Zhuravskaya N, *et al.* Functional, coronary anatomic and prognostic correlates of CFVR during SE. *J Am Coll Cardiol* 2019;**74**:2280–2293.
15. Ciampi Q, Zagatina A, Cortigiani L, Wierzbowska-Drabik K, Kasprzak JD, Haberka M, *et al.* Prognostic value of SE assessed by the ABCDE protocol. *Eur Heart J* 2021;**42**:3869–3878.
16. Mehra R, Tjurmina OA, Ajijola OA, Arora R, Bolser DC, Chapleau MW, *et al.* Research opportunities in autonomic neural mechanisms of cardiopulmonary regulation: a report from the national heart, lung, and blood institute and the national institutes of health office of the director workshop. *JACC Basic Transl Sci* 2022;**7**:265–293.
17. Fukuda K, Kanazawa H, Aizawa Y, Ardell JL, Shivkumar K. Cardiac innervation and sudden cardiac death. *Circ Res* 2015;**116**:2005–2019.
18. Huang PH, Leu HB, Chen JW, Wu TC, Lu TM, Ding YA, *et al.* Comparison of endothelial vasodilator function, inflammatory markers, and N-terminal pro-brain natriuretic peptide in patients with or without chronotropic incompetence to exercise test. *Heart* 2006;**92**:609–614.
19. Lauer MS. Chronotropic incompetence: ready for prime time. *J Am Coll Cardiol* 2004;**44**:431–432.
20. Abidov A, Hachamovitch R, Hayes SW, Ng CK, Cohen I, Friedman JD, *et al.* Prognostic impact of hemodynamic response to adenosine in patients older than age 55 years undergoing vasodilator stress myocardial perfusion study. *Circulation* 2003;**107**:2894–2899.
21. Bhatheja R, Francis GS, Pothier CE, Lauer MS. Heart rate response during dipyridamole stress as a predictor of mortality in patients with normal myocardial perfusion and normal electrocardiograms. *Am J Cardiol* 2005;**95**:1159–1164.
22. Lauer MS, Mehta R, Pashkow FJ, Okin PM, Lee K, Marwick TH. Association of chronotropic incompetence with echocardiographic ischemia and prognosis. *J Am Coll Cardiol* 1998;**32**:1280–1286.
23. Elhendy A, Mahoney DW, Khanderia BK, Burger K, Pellikka PA. Prognostic significance of impairment of heart rate response to exercise. Impact of left ventricular function and myocardial ischemia. *J Am Coll Cardiol* 2003;**42**:823–830.

24. Chaowalit N, Mc Cully RB, Callahan MJ, Mookadam F, Bailey KM, Pellikka PA. Outcomes after normal dobutamine SE and predictors of adverse events: long-term follow-up of 3014 patients. *Eur Heart J* 2006;**27**:3039–3044.
25. Cortigiani L, Carpeggiani C, Landi P, Raciti M, Bovenzi F, Picano E. Usefulness of blunted heart rate reserve as an imaging-independent prognostic predictor during dipyridamole-echocardiography test. *Am J Cardiol* 2019;**124**:972–977.
26. Aihara K, Kato Y, Suzuki S, Arita T, Yagi N, Semba H, *et al.* Prognostic value of the heart rate profile during exercise in patients with atrial fibrillation. *Eur J Prev Cardiol* 2018;**25**: 1634–1641.
27. Hobday TJ, Pellikka PA, Attenhofer Jost CH, Oh JK, Miller FA, Seward JB. Chronotropic response, safety, and accuracy of dobutamine stress echocardiography in patients with atrial fibrillation and known or suspected coronary artery disease. *Am J Cardiol* 1998;**82**: 1425–1427.
28. Cortigiani L, Carpeggiani C, Landi P, Raciti M, Bovenzi F, Picano E. Prognostic value of heart rate reserve in patients with permanent atrial fibrillation during dipyridamole stress echocardiography. *Am J Cardiol* 2020;**125**:1661–1665.
29. Jiménez-Marrero S, Ramos R, Comín-Colet J. Chronotropic incompetence: rediscovering phenotypes in heart failure with preserved ejection fraction. *Rev Esp Cardiol (Engl Ed)* 2023;**76**:497–499.
30. Cerracchio E, Campagnano E, Villari B, Ciampi Q. The revival of the electrocardiogram in the stress imaging era: what European society of cardiology 2024 guidelines say (and don't say). *Explor Cardiol* 2025;**3**:101256.