The Persistent Exclusion of Older Patients From Ongoing Clinical Trials Regarding Heart Failure

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Background: Much clinical research of relevance to elderly patients examines individuals who are younger than those who have the disease in question. A good example is heart failure. Therefore, we investigated the extent of exclusion of older individuals in ongoing clinical trials regarding heart failure.

Methods: In the context of the Increasing the Participation of the Elderly in Clinical Trials (PREDICT) study, data from ongoing clinical trials regarding heart failure were extracted from the World Health Organization Clinical Trials Registry Platform on December 1, 2008. Main outcome measures were the proportion of trials excluding patients by an arbitrary upper age limit or by other exclusion criteria that might indirectly cause limited recruitment of older individuals. We classified exclusion criteria into 2 categories: justified or poorly justified.

Results: Among 251 trials investigating treatments for heart failure, 64 (25.5%) excluded patients by an arbitrary upper age limit. Such exclusion was significantly more common in trials conducted in the European Union than in the United States (31/96 [32.3%] vs 17/105 [16.2%]; P = .007) and in drug trials sponsored by public institutions vs those by private entities (21/59 [35.6%] vs 5/36 [13.9%]; P = .02). Overall, 109 trials (43.4%) on heart failure had 1 or more poorly justified exclusion criteria that could limit the inclusion of older individuals. A similar proportion of clinical trials with poorly justified exclusion criteria was found in pharmacologic and nonpharmacologic trials.

Conclusion: Despite the recommendations of national and international regulatory agencies, exclusion of older individuals from ongoing trials regarding heart failure continues to be widespread.

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OLDER INDIVIDUALS ARE prone to develop heart failure (HF) because of the combination of age-related changes in the cardiovascular system and the high prevalence of cardiovascular diseases. Approximately 80% of all cases of HF occur in individuals 65 years and older, and because of the aging of the population, it is anticipated that the number of older adults with HF will double during the next 25 years in the United States. In this group, HF accounts for more hospital admissions than any other condition.

See also pages 544 and 559

Despite the importance of HF, there is a dearth of research specifically targeting older HF patients. Approximately 30% of relevant clinical trials (CTs) excluded older individuals and only 15% included patients older than 80 years. In addition, most CTs excluded older individuals as a result of indirect exclusion criteria based on the presence of comorbidities, polypharmacy, or reduced life expectancy. As such, older patients who participate in CTs are often not representative of those seen in clinical practice. This situation represents a clear challenge for physicians because limited information exists regarding the efficacy and safety of drugs and of nonpharmacologic interventions in older HF patients.

See Invited Commentary at end of article
Consequently, a European Commission–funded project entitled Increasing the PaRticipation of the ELDerly in Clinical Trials (PREDICT) (http://www.predictceu.org/) investigated the exclusion of older individuals from CTs. As part of this project, we analyzed the major characteristics of ongoing CTs using the online open-access CT registry platform maintained by the World Health Organization (WHO). The aims of this study were to assess the extent of underrepresentation of older individuals in ongoing CTs on HF, to evaluate the justifications for their exclusion, and to assess associations between trial characteristics and the exclusion criteria that have been applied.

### METHODS

Information regarding ongoing CTs was obtained on December 1, 2008, from the WHO International Clinical Trials Registry Platform (WHO-ICTRP) (www.who.int/trialsearch/AdvSearch.aspx). This database collects trials registered in the Australian New Zealand Clinical Trials Registry, the International Standard Randomized Controlled Trial Number Register (http://www.isrctr.org; a not-for-profit organization in the United Kingdom), the US Food and Drug Administration registry (http://clinicaltrials.gov), the Netherlands Trials Registry (http://www.trialregister.nl/trialreg/index.asp), and the Chinese Clinical Trials Registry (http://www.chictr.org/5 (ubifwz55mg0uhv55jxrlgo5))/Site/Search.aspx?lang=EN). Within this database, a search was performed for ongoing CTs regarding HF using the following keywords: heart failure, in the condition field; alf, in the register field; and recruiting, in the recruitment status field.

After a careful appraisal of the literature concerning the exclusion of older individuals from CTs, the principal investigators (A.C. and J.O.) identified the most relevant information to collect from the study protocol of each CT. Variables in CT design included the setting (unicenter or multicenter), geographic area (including 4 categories: United States with or without other countries, European Union with or without other countries, United States and European Union with or without other countries, and other countries neither in the European Union nor the United States), sponsorship (public or private), sample size, and duration of the trial and treatment (with 4 categories: pharmacologic trials, devices, educational-behavioral-lifestyle [EBL] interventions, and other treatments [this was a miscellaneous group of interventions such as surgery, telemonitoring, stem cell therapy, or pharmacist interventions]). Some of the categories of these variables were grouped (eg, pharmacologic vs nonpharmacologic trials, United States vs non–United States trials) for particular analyses.

Concerning exclusion criteria, we assessed the presence of an upper age limit (explicit exclusion) and other exclusion criteria that might potentially lead to a reduction in the number of older individuals included in the trials, such as exclusion by comorbidity, cognitive or physical impairment, reduced life expectancy, drug use, visual or hearing deficits, or inability to attend the follow-up. Exclusion by polypharmacy was applied to CTs using generic terms to exclude patients undergoing drug treatment or to CTs excluding patients treated with 3 or more classes of drugs.

### JUSTIFICATION OF EXCLUSIONS AND STATISTICAL ANALYSIS

Exclusion criteria were classified as justified or poorly justified according to a consensus reached by the principal researchers (A.C. and J.O.) based on an adaptation of a previous work (Table 1). Descriptive data are presented as numbers and percentages for categorical variables and mean or median for continuous variables. Univariate analyses consisted of the 2-sided t test or Mann-Whitney test for continuous variables and the \( \chi^2 \) test for categorical variables. All statistical tests were 2-tailed. Factors were considered statistically significant at \( P < .05 \).

Multivariate logistic regression modeling was performed to identify variables significantly associated with an explicit upper age exclusion. The dependent variable was coded using binary
and divided into 2 categories (1-100 and 101-500 patients) to determine the nature of its relationship with upper age exclusion. Forward and backward stepwise regressions were used to identify a set of independent variables that added significantly to the fit of the model. The logistic models were tested for goodness of fit with the Hosmer-Lemeshow test.

A similar multivariate logistic regression analysis was also applied to identify the variables associated with exclusion by cognitive impairment, using as independent variables those significantly associated with this exclusion criterion in the univariate analysis. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from each multivariate logistic regression model.

The models were validated by dividing the data into 2 subsets (trials starting in 2002-2006 vs those during 2007-2008), computing separate regression models for each subset, identifying the independent variables that proved to be significant in both models, and then applying a new logistic regression equation for the entire database using only those variables that exhibited stability in the 2 separate models. For all analyses, SPSS statistical software, version 17.0 (SPSS, Inc, Chicago, Illinois), was used.

### RESULTS

As of December 1, 2008, there were 378 registered trials recruiting patients with HF in the WHO-ICTRP. A total of 127 studies were excluded: 79 because of their observational design, 40 because HF was not the main target condition, 6 because they investigated the physiopathology of HF without proposing any treatment, 1 because it was registered twice, and 1 because it involved children. Our analysis focused on the remaining 251 CTs (66.4%). Most CTs (220 [87.3%]) were extracted from the US registry (www.clinicaltrials.gov). Most trials (150 [59.8%]) included patients with systolic or diastolic HF. One-third of CTs (87 [34.7%]) focused on the study of systolic HF, whereas 14 trials (5.6%) investigated diastolic HF only.

The main characteristics of ongoing CTs are described in Table 2. Most investigated nonpharmacologic interventions (156 [62.2%]), had unicheter settings (161 [64.1%]), and were sponsored by public institutions (155 [61.6%]). The highest number of trials originated in the European Union or the United States, so we specifically compared these 2 locations. Only 39 trials (15.5%) did not involve the European Union or the United States, having been developed in countries such as Canada, Australia, New Zealand, Japan, China, and Israel.

The total number of CTs and the proportion of those investigating drugs, devices, or other interventions were similar between trials performed in the United States and those in the European Union, but a higher proportion of EBL trials were performed in the United States compared with the European Union (24/105 [22.9%] vs 11/96 [11.5%]; P = .03). The frequencies of exclusion criteria that might limit the inclusion of older individuals in HF CTs are given in Table 3.

### OTHER EXCLUSION CRITERIA THAT MIGHT LIMIT THE PARTICIPATION OF OLDER INDIVIDUALS

We found that 64 CTs (25.5%) excluded patients by an upper age limit. The age varied between 65 and 95 years, with a median value of 80 years. The proportion of trials excluding by an upper age limit was 28.2% in the period 2002-2006 (n = 149) vs 21.6% in the period 2007-2008 (n = 102; P = .24). Trials excluding by an upper age limit had significantly smaller sample sizes than trials without this exclusion criterion (163 vs 560 patients; P = .001). Exclusion rates were higher for CTs testing drugs (26/95 [27.4%]) or EBL interventions (10/40 [25.0%]) than for CTs investigating devices (12/67 [17.9%]). Drug trials sponsored by public institutions had significantly higher rates of exclusion than drug trials sponsored by private entities (21/59 [35.6%] vs 5/36 [13.9%]; P = .02).

Exclusion by upper age limit was significantly more common in trials conducted in the European Union than in the United States (31/96 [32.3%] vs 17/105 [16.2%]; P = .007).
Almost half of pharmacologic trials performed in the European Union excluded patients by an upper age limit compared with less than one-tenth of those performed in the United States (16/33 [48.5%] vs 3/37 [8.1%]; P < .001).

Trials investigating EBL interventions also showed higher rates of exclusion by upper age limit in the European Union trials than in the US trials, although this difference was not statistically significant (5/11 [45.5%] vs 3/24 [12.5%]; P = .08). Exclusion by upper age limit was uncommon and similar between both geographic areas for trials investigating devices. We did not find statistically significant differences in age cutoffs among trials excluding by an explicit upper age limit according to their setting, sponsoring, treatment, or geographic area. The logistic regression analysis using sample size, sponsor, geographic area, and type of treatment as covariates identified only high sample size and US trials as independent factors associated with lower exclusion by upper age limits (ORUnited States vs other countries = 0.30; 95% CI, 0.16-0.59; ORsample > 100 vs ≤ 100 = 0.25; 0.13-0.47).

EXCLUSION OF PATIENTS BY COMORBID DISEASE

The most common exclusion criteria were those based on comorbidity (n = 201, 80.1% of CTs). Exclusion by specific comorbidities, such as renal or liver disease, was observed in 190 CTs (75.7%), whereas 26 CTs (10.4%) excluded patients by comorbidity expressed in generic terms (ie, without mentioning any specific disease). Comorbidities that were commonly excluded are listed in Table 3. The mean number of excluded medical conditions was 3.3. The number of comorbidities excluded was higher in multicenter than in unicenter CTs (4.2 vs 2.9; P = .002) and in pharmacologic trials vs nonpharmacologic trials (4.3 vs 2.7; P < .001).

Overall, 16 CTs (6.4%) excluded patients based on a poorly justified generic comorbidity criterion. The information provided by the WHO-ICTRP was insufficient to allow the analysis of the justification of exclusions by specific comorbidities.

OTHER EXCLUSION CRITERIA THAT MIGHT LIMIT THE PARTICIPATION OF OLDER INDIVIDUALS IN CTs

Exclusion by Reduced Life Expectancy

In 91 CTs (36.3%), patients were excluded by reduced life expectancy. This exclusion criterion was more common in multicenter than in unicenter trials (43/90 [47.8%] vs 48/161 [29.8%]; P = .005) and in trials performed in the United States compared with those in the European Union (45/105 [42.9%] vs 26/96 [27.1%]; P = .02). Nonpharmacologic CTs also had a higher exclusion rate than pharmacologic trials (71/156 [45.5%] vs 20/95 [21.1%]; P < .001).

Exclusion by Cognitive Impairment

Some CTs excluded patients by cognitive impairment (32 [12.7%]). This exclusion criterion was more common in trials sponsored by public funding agencies (15/155 [16.1%] vs 7/96 [7.3%]; P = .04) and more common in EBL interventions (16/40 [40.0%]) than in trials regarding devices (3/67 [4.5%]; P < .001) or pharmacologic treatments (7/95 [7.4%]; P < .001). Exclusion by cognitive impairment was also more common in US trials than in European Union trials (20/105 [19.0%] vs 5/96 [5.2%]; P = .003). In the logistic regression analysis, using as independent variables those significantly associated with this exclusion criterion in the univariate analysis (sponsor, treatment, and geographic area), we found that only EBL treatments were significantly associated with exclusion by cognitive impairment (OREBL vs drug trials = 8.38; 95% CI, 3.09-22.70). Exclusion based on cognitive impairment was considered to be poorly justified in 12 trials (4.8%) (Table 4).

Exclusion by Use of Drugs

Approximately one-fifth of the CTs on HF (47 [18.7%]) excluded patients by concomitant use of drugs. Moreover, exclusion by polypharmacy was observed in 14 trials (5.6%). Poorly justified exclusion by use of drugs was observed in 18 trials (7.2%). Pharmacologic trials had significantly higher rates of poorly justified exclusions of patients by concomitant use of drugs than nonpharmacologic CTs (12/95 [12.6%] vs 6/156 [3.8%]; P < .009) (Table 4).

Exclusion by Physical Impairment

Exclusion by physical impairment was observed in 35 CTs (13.9%). Most such trials did so by excluding patients who were unable to walk or to perform exercise testing (29 [11.6%]). Five CTs (2.0%) excluded patients by ge-

Table 3. Frequencies of Exclusion Criteria That Might Negatively Affect the Inclusion of Older Individuals in Ongoing Clinical Trials Regarding Heart Failure

<table>
<thead>
<tr>
<th>Exclusion Criterion</th>
<th>Frequency, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper age limit</td>
<td>64 (25.5)</td>
</tr>
<tr>
<td>Reduced life expectancy</td>
<td>91 (36.3)</td>
</tr>
<tr>
<td>Total comorbidity</td>
<td>201 (80.1)</td>
</tr>
<tr>
<td>Generic</td>
<td>26 (10.4)</td>
</tr>
<tr>
<td>Specific</td>
<td>190 (75.7)</td>
</tr>
<tr>
<td>Specific disease exclusions</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>100 (39.8)</td>
</tr>
<tr>
<td>Liver</td>
<td>54 (21.5)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>73 (29.1)</td>
</tr>
<tr>
<td>Lung</td>
<td>61 (24.3)</td>
</tr>
<tr>
<td>Cancer</td>
<td>42 (16.7)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>22 (8.8)</td>
</tr>
<tr>
<td>Other</td>
<td>85 (33.9)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>32 (12.7)</td>
</tr>
<tr>
<td>Physical disability</td>
<td>35 (13.9)</td>
</tr>
<tr>
<td>Exclusion by drug treatment</td>
<td>47 (18.7)</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>14 (5.6)</td>
</tr>
<tr>
<td>Specific drug treatment</td>
<td>46 (18.3)</td>
</tr>
<tr>
<td>Inability to attend follow-up meeting</td>
<td>24 (9.6)</td>
</tr>
<tr>
<td>Hearing or visual deficits</td>
<td>11 (4.4)</td>
</tr>
<tr>
<td>Communication barriers</td>
<td>5 (2.0)</td>
</tr>
</tbody>
</table>

*Clinical trials using general terms to exclude patients receiving drug treatment or excluding patients receiving treatment with drugs belonging to 3 or more different pharmacologic groups.

**Table 4**
Table 4. Frequencies of Poorly Justified Exclusion Criteria That Might Negatively Affect the Inclusion of Older Individuals in Heart Failure Trials

<table>
<thead>
<tr>
<th>Exclusion Criterion</th>
<th>Poorly Justified Exclusions, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pharmacologic</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Upper age limit</td>
<td>26 (27.4%)</td>
</tr>
<tr>
<td>Reduced life expectancy</td>
<td>0</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
</tr>
<tr>
<td>Generic</td>
<td>8 (8.4%)</td>
</tr>
<tr>
<td>Specific</td>
<td>NA</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>4 (4.2%)</td>
</tr>
<tr>
<td>Physical disability</td>
<td>8 (8.4%)</td>
</tr>
<tr>
<td>Drug use^a</td>
<td>12 (12.6%)</td>
</tr>
<tr>
<td>Inability to attend</td>
<td>0</td>
</tr>
<tr>
<td>follow-up meeting</td>
<td></td>
</tr>
<tr>
<td>Hearing or visual deficits</td>
<td>0</td>
</tr>
<tr>
<td>Communication barriers</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Any unjustified exclusion</td>
<td>42 (44.2%)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

^aP = .009.
^bP = .15.

Other Exclusion Criteria

Inability to attend a follow-up visit was a reason for exclusion of patients in 24 CTs (9.6%). This criterion was more common, although the difference did not reach statistical significance in nonpharmacologic trials (19/156 [12.2%] vs 5/95 [5.3%; P = .07]). Only 1 trial excluded female patients. Exclusion by language barrier or visual/hearing impairment was found in 5 CTs (2.0%) and 11 CTs (4.4%), respectively. Exclusion by language barrier was considered poorly justified in all the cases, whereas poorly justified exclusions by visual or hearing impairment were observed in 3.6% of CTs.

Summary of Poorly Justified Exclusion Criteria

The frequencies of poorly justified exclusion criteria are summarized in Table 4. Almost half of the CTs (109 [43.4%]) had at least 1 poorly justified exclusion criterion, with similar proportions in pharmacologic and nonpharmacologic trials. Although poorly justified exclusion criteria were present in all types of trials, EBL interventions were associated with higher rates of such criteria than trials regarding other types of interventions (23/40 [57.5%] vs 86/211 [40.8%; P = .05]), whereas trials regarding devices were associated with lower rates (20/67 [29.9%] vs 89/184 [48.4%; P = .009). We did not find significant differences in the rate of trials with poorly justified exclusion criteria between those sponsored by industry compared with public trials or between those performed in the European Union or the United States.

The aims of the PREDICT study were to investigate the extent of exclusion of older individuals from CTs, to identify the reasons underlying this exclusion, and to produce a charter to champion the rights of older individuals to participate in CTs (www.predictieu.org). As part of this project, we analyzed the exclusion criteria of ongoing CTs on HF registered in the WHO database to verify whether older patients continue to be excluded from CTs, as previously reported. We found that a significant proportion of trials (n=64, 25.5%) are still limiting the participation of older patients using an arbitrary upper age limit, with similar figures to those observed in 1985-1989, 1990-1994, and 1995-1999 (21%, 35%, and 27%, respectively). Therefore, CTs that will influence clinical practice in the near future continue to discriminate against older individuals.

Ongoing drug trials regarding HF promoted by public institutions have significantly higher exclusion rates based solely on age compared with those sponsored by industry. In contrast, van Spall et al noted that CTs sponsored by the pharmaceutical industry had a higher rate of exclusion by age. This discrepancy might have been caused by the different methods used in our investigation, or it could reflect a real change with better implementation of the recommendations of the regulatory agencies in private companies than in public centers.

There was a lower rate of exclusion by an upper age limit in drug trials conducted in the United States than those in the European Union. A similar finding was observed in a study concerning published trials regarding statins. In this study, it was suggested that the Revitalization Act of 1993, a US law requiring the inclusion of women and minorities in drug trials conducted in the United States than those in the European Union, may explain at least part of this difference.

There is less evidence of the exclusion of older HF patients from CTs of nonpharmacologic intervention. However, in these trials, we found that poorly justified exclusion criteria were present in similar proportions to those in place in pharmacologic trials.

In addition, we found high rates of other exclusion criteria, such as the presence of comorbidity, cognitive impairment, physical disabilities, polypharmacy, communication barriers, or visual or hearing deficits, that might indirectly limit the inclusion of older individuals. We also examined whether exclusion criteria might be considered justified within each CT. To this purpose, we applied a modification of the criteria based on those presented by Van Spall et al, who found that 84% of CTs published in high-impact journals had at least 1 poorly justified exclusion criterion. In our study, we found that a lower percentage of CTs had at least 1 poorly justified exclusion criterion (109 [43.4%]). This difference might be explained by the limited amount of information provided by the WHO database, which did not allow us to...
evaluate the justification of the exclusion by specific co-morbidities, the most common exclusion criterion.

Randomized CTs are considered to stand at the pinnacle of the research method hierarchy for assessment of new interventions. However, their restrictive eligibility criteria may compromise their external validity. There are legitimate reasons for these practices because this approach generates a more homogeneous sample and allows for smaller, shorter, less expensive trials. However, there is a price to be paid for this decision because it also increases the likelihood of excluding many patients, particularly when older populations are concerned. Efficacy trumps effectiveness, and as a result, the physician often is not sure how best to approach the typical older HF patient.

Strong evidence exists that some categories of patients, such as older patients, are often excluded from CTs, with the result that the patients who participate in CTs are different from those seen in daily practice. This factor might reduce the usefulness of the information provided by CTs in the treatment of patients and even undermine the validity of clinical guidelines based on the best available evidence for the treatment of a specific disease. In addition, because of the longer life expectancy of women in developed countries, exclusion of older individuals has an indirect negative effect on women participating in CTs. The discrepancy between the patients evaluated in most CTs and the “real” patient population is particularly marked in the field of HF, a condition common in older age. Patients included in HF trials tend to be younger, are more often male, tend to have minimal comorbidity, and tend to take fewer medications than patients with HF usually seen in clinical practice. Therefore, only a few hospitalized older patients with HF would fulfill the eligibility criteria of some landmark CTs demonstrating the benefits of new drugs in improving the outcome of HF patients. In recent years, the situation did not significantly change because only 2 large CTs specifically targeted older HF patients.

Our study has some limitations. First, it analyzed the eligibility criteria of CTs restricted to the WHO-ICTRP registry. Although this group includes several different registries, the proportion of ongoing trials worldwide that are recorded in it is not known. Moreover, the information about each trial is limited, presenting only a brief summary of the trial protocol. As such, important data relevant to our research question might be lacking. Finally, we examined eligibility criteria in trial protocols, but we cannot know how many eligible patients will be excluded from the completed CTs because it is well known that other factors related to the investigators and the patient can influence participation in clinical research. This study also has certain strengths. First, the sample of CTs evaluated is large compared with those of previous studies in this area. Moreover, our results are not influenced by the publication bias that may affect previous reports based on published trials. The high proportion of nonpharmacologic trials in our study is noteworthy compared with a higher prevalence of pharmacologic studies in the series published in the literature.

The best solutions for the problem of older individuals’ exclusion from trials of clinical relevance to them are neither easy to identify nor straightforward to imple-
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Author Contributions: Drs Cherubini and Oristrell contributed equally to the manuscript. Drs Cherubini, Oristrell, Crome, and Lesauskaite had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Cherubini, Oristrell, Mills, Sinclair-Cohen, Clarfield, Szczerbinska, Edbrooke, and Hertogh. Acquisition of data: Ruggiero, Ferretti, Pla, and Diestre. Analysis and interpretation of data: Cherubini, Oristrell, Crome, Ruggiero, Ferretti, Pla, Diestre, Clarfield, Hertogh, Lesauskaite, Prada, and Topinkova. Drafting of the manuscript: Cherubini, Oristrell, Clarfield, Mills, Sinclair-Cohen, Lesauskaite, Prada, and Topinkova. Critical revision of the manuscript for important intellectual content: Cherubini, Oristrell, Mills, Clarfield, Crome, Hertogh, Lesauskaite, Szczerbinska, Edbrooke, Ruggiero, Ferretti, and Diestre. Statistical analysis: Oristrell, Hertogh, Prada, Szczerbinska, Ruggiero, Ferretti, Pla, Diestre, and Clarfield. Obtained funding: Mills, Sinclair-Cohen, Crome, Prada, Lesauskaite, Topinkova, and Edbrooke. Administrative, technical, or material support: Mills, Sinclair-Cohen, and Edbrooke. Study supervision: Cherubini, Oristrell, Mills, Crome, and Edbrooke.

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