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## **Determining the minimal clinically important difference for the six-minute walk test and the 200-meter fast-walk test during cardiac rehabilitation program in coronary artery disease patients after acute coronary syndrome.**

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1                   **DETERMINING THE MINIMAL CLINICALLY IMPORTANT**  
2                   **DIFFERENCE FOR THE SIX-MINUTE WALK TEST AND THE 200-**  
3                   **METER FAST WALK TEST DURING CARDIAC REHABILITATION**  
4                   **PROGRAM IN CORONARY ARTERY DISEASE PATIENTS AFTER**  
5                   **ACUTE CORONARY SYNDROME**

6  
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14  
15  
16                   Walk tests are often used in the assessment of functional capacity in patients with  
17                   pulmonary and cardiac diseases <sup>1</sup>. They require less technical expertise than laboratory tests <sup>2</sup>,  
18                   are inexpensive and easy to administer, and employ an activity that individuals perform on a  
19                   daily basis, *i.e.* walking <sup>3</sup>. The 6-Minute Walk Test (6MWT) is the most validated field test in  
20                   cardiorespiratory diseases <sup>4</sup>, and is widely used to assess functional exercise capacity and  
21                   prognosis since it is reproducible and well tolerated in patients with chronic heart failure  
22                   (CHF) <sup>2,5</sup> and with CAD <sup>6</sup>. Recent data showed that, in CAD patients, this test is submaximal

23 exercise, approximately corresponding to the first ventilatory threshold (VT) <sup>6, 7</sup>. It can be  
24 performed early after a myocardial infarction (MI) <sup>8</sup>, and can be used to assess cardiac  
25 rehabilitation programs <sup>9, 10</sup>.

26 The 200-Meter Fast Walk Test (200MFWT) has recently been developed in healthy  
27 elderly people and in CAD patients <sup>7, 11</sup>. It has also been used to assess improvements in  
28 functional capacity after a training program in elderly <sup>12</sup> and CAD patients <sup>7</sup>. The 200MFWT  
29 explores higher exercise intensities than does the 6MWT, both of which could be of interest  
30 in cardiac rehabilitation. Indeed, recent studies suggest that vigorous exercise training and/or  
31 high intensity aerobic interval exercise may be superior to moderate intensity exercise in that  
32 they increase aerobic capacity to a greater extent in CAD patients <sup>13, 14</sup>.

33 Field walk tests are objective measures that provide a means to monitor response to  
34 treatment <sup>3</sup>. The interpretation of functional changes can guide clinical management and can  
35 be primary endpoints in interventional or observational studies. It is thus important to  
36 determine whether a change in function is clinically relevant or not. One method to answer  
37 this question quantitatively is to determine the minimal clinically important difference  
38 (MCID) for the test used.

39 The Minimal Clinically Important Difference (MCID) is a concept defined as “the smallest  
40 difference in score in the domain of interest which patients perceive as beneficial and which  
41 would mandate, in the absence of troublesome side effects and excessive cost, a change in the  
42 patients management” <sup>15</sup>. The MCID is different from the Minimal Detectable Change, that  
43 indicates the amount of change required to exceed measurement variability <sup>16, 17</sup>. Indeed,  
44 when interpreting clinical measures, it is important to consider that, even though small  
45 changes may be statistically significant, they may not be clinically relevant <sup>16, 18</sup>. MCID  
46 values are therefore important to appreciate the clinical relevance of observed changes, at

47 both the individual and group levels. As individuals interpret “meaningful change”  
48 differently, depending on a multitude of factors (e.g. prior level of function, age, physical  
49 environment ), the MCID is a dynamic and context-specific concept, and derivations of the  
50 MCID are usually estimated only for a specific population at a particular stage of recovery <sup>19</sup>.  
51 Because estimation of the MCID is a process evolving from multiple perspectives, it is  
52 important to estimate the MCID for key clinical outcome measures, such as walking ability in  
53 CAD patients. Indeed, walking is one of the most basic human motor activities and plays a  
54 key role in patients’ participation.

55 Numerous methods to derive the MCID have been described <sup>15, 16, 20-23</sup>. They are  
56 usually divided into 2 categories: distribution-based and Anchor-based <sup>21</sup>.

57 Anchor-based methods involve comparing a patient’s change score with another  
58 measure of clinically relevant change <sup>24</sup>. In this method, an external criterion of change is  
59 compared with another measure of change. An example of external criterion may be the  
60 change perceived by the patient or clinician <sup>16, 25</sup>(e.g. self-perceived improvement in walking  
61 ability). The other measure of change used for comparison is usually an objective data, such as  
62 walking distance. Anchor based methods have the advantage of being more clearly  
63 understood because change are related to a clear clinical observation <sup>26</sup>. This helps to  
64 determine that a change is considered important to the patient, physician or researcher, and  
65 even the health care authorities or society at large <sup>27</sup>.

66 Distribution-based methods, such as the standard error of the measure (SEM) <sup>28</sup> and  
67 the effect size <sup>29</sup>, are built on the statistical and psychometric properties of the measure in a  
68 population. Concurrent use of the two approaches is recommended to evaluate the effects of  
69 the methodology on the final value <sup>30</sup>.

70           There is as yet no accepted threshold for clinically significant change in cardiac  
71 diseases in the 6MWT walked distance (6MWD)<sup>31</sup>, nor in the 200MFWT time  
72 (200MFWTT).

73           The aims of this study were (1) to prospectively determine the MCID for the 6MWD  
74 and the 200MFWTT in patients with CAD and (2) to determine if there was any difference  
75 between the MCID determined by patients and those assessed by their therapists.

76

77

## 78 **METHODS**

### 79 **Participants**

80           Patients who were referred to the cardiac rehabilitation department of Dijon University  
81 Hospital following an acute coronary syndrome were invited to participate. Patients were  
82 eligible if they had been admitted to an ambulatory cardiac rehabilitation program after  
83 percutaneous transluminal coronary angioplasty or coronary stenting, following an acute  
84 coronary syndrome. Only patients admitted within 2 months after the acute coronary  
85 syndrome, under optimal medical treatment according to the latest recommendations<sup>32</sup> (i.e.  $\beta$ -  
86 blockers; Angiotensin converting enzyme inhibitors or Angiotensin receptor blockers, anti-  
87 platelet agents, statins) were included, with no restrictions regarding body mass index. All  
88 gave their written consent after being clearly advised about the protocol, which had been  
89 approved by the Institutional Ethics Committee and conformed to the principles outlined in  
90 the Declaration of Helsinki. Exclusion criteria were: residual myocardial ischemia or unstable  
91 angina; chronic heart failure, defined by (a) Framingham clinical criteria<sup>33</sup>, (b) a left  
92 ventricular ejection fraction <45%, measured by echocardiography using the Simpson  
93 method; severe valve disease; diabetes; pulmonary hypertension); chronic respiratory

94 insufficiency; symptomatic lower limb artery disease; severe renal insufficiency; and any  
95 associated deficiency such as severe orthopaedic troubles limiting use of the lower limbs and  
96 that were more limiting to effort than the cardiac disease itself.

## 97 **Protocol**

98 All patients received an 8-week cardiac rehabilitation program that included two  
99 components:

100 - Personalised training tailored on the basis of the results of a stress test, performed on  
101 treadmill using the Bruce modified protocol <sup>34</sup>, before entering the rehabilitation programme  
102 <sup>41</sup>, and individualized on the basis of preliminary physical activity habits, determined using  
103 the Dijon physical activity score questionnaire <sup>11</sup>. The training intensity was prescribed at a  
104 target heart rate (HR) zone derived from the maximal HR at the end of the stress test. It was  
105 calculated using the Karvonen formula <sup>35</sup> as follows: training HR = rest HR + 75% (max HR  
106 – rest HR). During training sessions, Borg scale with level 6 to 20 was also used <sup>36</sup>. The  
107 target was set between 13 and 15.

108 - Individual and group educational interventions based on the patient's risk factors <sup>37</sup>.

109 The training program was in line with the latest recommendations in the field <sup>37-39</sup>,  
110 and consisted of one-and-a-half-hour sessions, 3 days a week over 8 weeks. Patients had to  
111 perform two 30-minute sessions of two different aerobic exercises (walking and bicycle or  
112 arm cycling) with a global warm up and cool down, and 20 minutes of circuit weight training  
113 adapted to each patient's capacities (solicited muscles groups were leg extensors and flexors,  
114 ankle dorsiflexors and plantar-flexors, elbow flexors and extensors, Latissimus dorsi).

115 Patients performed stress tests and walk tests as usual at the beginning and at the end of  
116 the rehabilitation program. The initial walk tests were performed 2 to 4 days after the ET. During

117 this interval, all patients performed a trial run of each walk test to familiarize them with the test  
118 and the path. They were repeated at the 6<sup>th</sup> and 12<sup>th</sup> training session. After each evaluation, and  
119 before giving the result of the test, the physiotherapist asked the patients the following question  
120 “Has there been any change in your walking ability since the last walking tests” ? The responses  
121 were made on a 9-level Likert scale, with a score of 0 indicating no change, positive scores  
122 indicating improvement, and negative scores indicating worsening walking ability. Change was  
123 scored as follows: (-4): much worse; (-3): worse; (-2): slightly worse, meaningful; (-1): very  
124 slightly worse, not meaningful; (0): Unchanged; (1): very slightly better, not meaningful; (2):  
125 slightly better, meaningful; (3) : better; (4): much better.

126 In order to study inter-observer agreement between the patient and his therapist, the  
127 same question was asked to the physiotherapist supervising the patient’s training, using the  
128 same 9-level scale. All ratings were completed before giving the result of the tests to ensure  
129 that both participants and clinicians were blinded to the performance, as recommended for the  
130 assessment of change in subjects in MCID studies <sup>15</sup>.

131 During the walk-tests, patients wore a telemetric device (Teleguard, GE Medical  
132 Systems, Denmark). Blood pressure was measured before and immediately after each test in  
133 the left arm using a standard cuff mercury sphygmomanometer. Patients were also asked to  
134 rate their dyspnea on a Borg scale at the end of each test, and any clinical symptoms such as  
135 angina were recorded. Both walk tests were supervised by a physiotherapist blinded to the  
136 stress-test results and to the training group of the patient.

137 The 6MWT was performed on a 50-meter unobstructed path. The patients were  
138 instructed to walk at a self-selected pace from one end of the path to the other and back, in  
139 order to cover as much distance as they could during the allotted time. The time was called  
140 out every 2 minutes. Standard encouragement at 30-second intervals was provided. Slowing  
141 down and stopping to rest were permitted. At the end of 6 minutes, the total distance walked

142 in meters (m) was measured. These technical aspects are in line with the American Thoracic  
143 Society recommendations for the 6-minute walk test<sup>40</sup>.

144 The 200-meter fast walk test consisted of walking twice up and down the 50-m long  
145 path in the hospital corridor as fast as possible, without running. Standard encouragement was  
146 provided at mid-distance. Slowing down and stopping to rest were permitted. The time taken  
147 to perform the test was measured in seconds<sup>7, 11</sup>.

148

## 149 **Statistical Analyses**

150 Change in walking distance (for the 6MWD) and in time (for the ) were expressed as  
151 an absolute distance or time, by subtracting the initial result from the discharge result.

152 For the anchor-based approach, patients were dichotomized based on their self  
153 assessment of clinical change. A cutoff of 2 (slightly better, meaningful) was used to identify  
154 patients who achieved an MCID (score  $\geq 2$ ) from those who did not (score  $<2$ ). As previously  
155 described, the mean score change for the smallest meaningful change (*i.e.*  $\geq 2$ ) was taken as  
156 the MCID for both walk tests<sup>41, 42</sup>. Then, the means of those subjects who achieved an MCID  
157 were compared with those who did not using a one-way ANOVA. The positive predictive  
158 value (PPV), negative predictive value (NPV), sensitivity and specificity for change in the  
159 6MWD and in 200MFWTT were calculated and a Receiver Operating Characteristic (ROC)  
160 curve obtained. Given the objective of this work, *i.e.* to estimate the minimal improvement in  
161 the 6MWD or in the 200MFWTT that would lead the patient to be satisfied with his outcome,  
162 we chose to consider PPV and NPV rather than sensitivity and specificity to identify the  
163 MCID of these tests.



164 This analysis was repeated with patients dichotomized according to their  
165 physiotherapist's assessment of clinical change, in order to identify the MCID from the  
166 therapist's point of view. The same cutoff of 2 (slightly better, meaningful) was used to  
167 distinguish between patients who achieved an MCID and those who did not.

168 Concerning the distribution-based methods, we used the SEM to estimate the MCID.  
169 The SEM is defined as  $\sigma_1 \times \sqrt{1-r}$ , where  $\sigma_1$  is the baseline standard deviation and  $r$  is the  
170 test-retest reliability. One SEM is supposed to be a close approximation of the MCID<sup>28</sup>. The  
171 intraclass correlation coefficients used for test-retest reliability were calculated from data of a  
172 previous study<sup>7</sup>, and were set at 0.71 for the 6-MWT and 0.87 for the 200-MFWT.

173 Agreement between the ratings of patients and physiotherapists was studied using  
174 Cohen's  $\kappa$  correlation coefficient. Coefficients from 0 to 0.4 reflect a weak association, 0.4 -  
175 0.75 a moderate association, and above 0.75 a strong association<sup>43</sup>.

176 Improvement in maximal exercise capacity between patients achieving MCID and  
177 those who did not were compared using a Student t-test, and correlations between  
178 improvement in 6MWD and improvement in maximal exercise capacity were tested using  
179 Pearson correlation coefficient.

180 Data were recorded using Excel® software for Windows, and statistical analysis was  
181 performed using NCSS 2004® for Windows. The threshold for significance was set at  
182  $p < 0.05$ .

### 183 **Sample Size**

184 As walk tests are usually performed only at the beginning of the rehabilitation program and at  
185 discharge, we could not calculate an estimated sample size based on the evolution of  
186 performance in tests repeated every 2 weeks. According to the latest studies concerning

187 MCID in the 6MWD in COPD and post-stroke functional measures<sup>41, 42, 44</sup>, and anticipating a  
188 10% dropout from the program, we initially planned to include 80 patients.

189

## 190 **RESULTS**

### 191 **Participants**

192 Eighty-one patients were recruited, and all of them completed the rehabilitation  
193 program. Two patients did not complete the 3rd evaluation (both had to stop training for 2  
194 weeks for personal or family reasons). The demographic and anthropometric characteristics of  
195 the 81 included patients are described in table 1.

196

### 197 **Walk tests and maximal exercise tests results**

198 Overall, there was a mean improvement of  $73.2 \pm 56.5$  meters in the 6MWD ( $15.7 \pm$   
199  $12.2\%$ ), and of  $5 \pm 17.7$  seconds in the 200-MFWT time ( $-5.3 \pm 10.8\%$ ) (figure 1). All of the  
200 walk tests were well tolerated both before and after rehabilitation, and were performed  
201 without being prematurely interrupted or stopped. No significant arrhythmias were observed  
202 on the telemetric device recordings. The mean rate of perceived exhaustion for the 6MWT  
203 and the 200MFWT were  $14.9 \pm 0.8$  and  $16 \pm 0.9$  before, and  $14.6 \pm 0.9$  and  $16.1 \pm 1$  after,  
204 respectively. All patients significantly improved maximal exercise capacity from  $7.2 \pm 1.7$   
205 METS at baseline to  $9 \pm 2.1$  METs at the end of the training period (mean improvement  $25 \pm$   
206  $13.8\%$  %,  $p < 0.01$ ), without significant change in the maximal heart rate ( $121.2 \pm 13.8$  and  
207  $126.4 \pm 16$ , respectively). There were no significant difference in the improvement of  
208 maximal exercise capacity between those patients who achieved MCID and those who  
209 did not between the 2<sup>nd</sup> and 3<sup>rd</sup> walk tests (mean improvement:  $+ 26.4 \pm 10.2\%$  Vs  $+ 24.7$

210  $\pm 15.4\%$ , respectively). Finally, improvement in 6MWD and in maximal exercise capacity,  
211 expressed in METs, were moderately correlated ( $r= 0.59, p<0.05$ )

212

### 213 **Anchor-Based Estimation of the MCID**

214 The distribution frequency of the change scores concerning walking ability, from the  
215 patients' point of view, between the initial and the 2<sup>nd</sup> evaluation, as well as between the 2<sup>nd</sup>  
216 and the 3<sup>rd</sup>, and the 3<sup>rd</sup> and the final evaluation, are shown in figure 2. The distribution was  
217 best balanced between the 2<sup>nd</sup> and 3<sup>rd</sup> evaluation. We thus considered that this period of the  
218 rehabilitation program (between the 6<sup>th</sup> and 12<sup>th</sup> training session) was the best suited for the  
219 calculation of the MCID, since during this period the assessments of the patients varied the  
220 most widely. Seventy-nine patients completed the 2<sup>nd</sup> and 3<sup>rd</sup> evaluation.

221 At this time, 40 patients rated themselves as  $\geq 2$ , while 39 reported little or no  
222 improvement, or even a worsening of perceived walking ability (score  $<2$ ). The mean change  
223 in the 6MWD in those participants who classified themselves as improved was  $+ 23.3 \pm 34.8$   
224 meters, compared with  $- 6.5 \pm 31$  meters in those who reported a small change or worsening  
225 (figure 3, A). The mean change in the 200MFWTT in those who classified themselves as  
226 improved was  $- 1.4 \pm 6.8$  seconds, vs.  $+ 0.1 \pm 4.8$  seconds in those who reported little or no  
227 change, or worsening. There was a significant difference between the 2 groups for the 6MWD  
228 ( $p< 0.001$ ) whereas no significant difference was found for the 200MFWTT ( $p=0.26$ ).

229 The PPV and NPV, sensitivity and specificity for the 6MWD and the 200MFWT  
230 using patients' rating of change are reported in table 2. Concerning the 6MWD, for an  
231 MCID between 21 and 27m, the PPV ranged between 0.8 and 0.9, and the NPV ranged  
232 between 0.63 and 0.66 (table 2, A). An MCID of 25 meters corresponded to a sensitivity of  
233 0.55 and a specificity of 0.92, with an area under the curve (AUC) of 0.78 (95% CI: 0.65 –

234 0.86). Concerning the 200MFWT, for an MCID between -1 and -6 seconds, the PPV and  
235 NPV were poor, ranging from 0.45 to 0.47, and from 0.33 to 0.41, respectively (table 2, B).  
236 An MCID of -2 seconds corresponded to a sensitivity of 0.67 and a specificity of 0.14 (AUC :  
237 0.4; 95% CI: 0.27 - 0.53) (Figure 4).

238         Concerning the physiotherapists' ratings, 58 patients were rated  $\geq 2$  and 21 rated  $< 2$ .  
239 The mean change in the 6MWD in the patients classified as improved by the physiotherapist  
240 ( $\geq 2$ ) was  $+ 15.2 \pm 4.6$  meters, compared with  $- 9.9 \pm 7.6$  meters in those who were classified  
241 as stable or worsened ( $< 2$ ) (figure 3, B). The mean change in 200MFWTT in those judged as  
242 improved was  $- 1.3 \pm 1.2$  seconds, vs.  $+ 1.04 \pm 1$  seconds in those judged little improved or  
243 stable or worsened. There was a significant difference between the 2 groups for the 6MWD  
244 ( $p < 0.01$ ) whereas no significant difference was found for the 200-MFWT performance ( $p =$   
245 0.12).

246         The PPV and NPV, sensitivity and specificity for the 6MWD and the 200MFWTT  
247 using physiotherapists' rating of change are reported in table 3. Concerning the 6MWD, for  
248 an MCID between 15 and 27m, the PPN ranged between 0.84 and 0.95, and the NPV ranged  
249 between 0.34 and 0.38. An MCID of 25 meters corresponded to a sensitivity of 0.41 and a  
250 specificity of 0.95 (AUC: 0.7; 95% CI: 0.55 -0.81). Concerning the 200MFWTT, for an  
251 MCID between -1 and -6 seconds, the PPN ranged between 0.68 and 0.71, and the NPV  
252 ranged between 0.11 and 0.2. An MCID of -2 seconds corresponded to a sensitivity of 0.67  
253 and a specificity of 0.14, (AUC: 0.38; 95% CI :0.22 -0.5).

254         Cohen's  $\kappa$  correlation coefficient between patients' and physiotherapists' judgment  
255 was 0.17 for the 6-MWD and 0.29 for the 200-MFWTT, reflecting poor agreement.

256         When considering patients who rated themselves  $< 2$ , 16 were considered stable or  
257 worsened by the physiotherapist (score  $< 2$ ), and 23 were considered improved (score  $\geq 2$ )

258 (table). There was no significant difference between patients classified  $<2$  and those classified  
259  $\geq 2$  by the physiotherapist for either the 6MWD or the 200MFWTT (table 4). Moreover, there  
260 was also no significant difference in the HR variation between the 2 evaluations for the 2  
261 groups (table 4).

262

### 263 **Distribution-Based Estimation of the MCID**

264 When considering the patients' self assessment, the SEM for the 6MWD was 23  
265 meters using the baseline standard deviation for the 6MWD and an intraclass correlation  
266 coefficient of 0.71. Concerning the 200MFWT, using an intraclass correlation coefficient of  
267 0.87 the SEM for the 200MFWTT was - 4.2 seconds.

268 Using the same methodology with the physiotherapists' judgment, the SEM was 36  
269 meters for the 6MWD and -5.5 seconds for the 20MFWT.

270 Overall, 76 out of 81 patients achieved an improvement of over 25 meters in the  
271 6MWD. When considering the progression between the 2<sup>nd</sup> and 3<sup>rd</sup> evaluation, 23 had  
272 improved the 6MWD by over 25 meters, whereas 54 had improved by less than 25 meters.  
273 There was no difference in the initial 6MWD among patients who achieved the MCID ( $491 \pm$   
274  $55$  meters) and those who did not ( $486 \pm 56$  meters).

275

## 276 **DISCUSSION**

277 We estimated the MCID for the 6MWD at approximately 25 meters among CAD  
278 patients who recently suffered an ACS and who had benefited from cardiac rehabilitation.  
279 This estimate was consistent, whatever the estimation method used (anchor-based or

280 distribution-based). Using the same methodology, we could not determine an MCID with  
281 satisfactory metrological qualities for the 200MFWTT.

282 To our knowledge, this is the first study to evaluate the MCID for walk tests among  
283 CAD patients. A previous study determined an MCID for the health status in patients with  
284 heart disease, but considered health-related quality of life scores, and used a different  
285 approach, based on a consensus reached by a panel of physicians <sup>45</sup>. Here, we used a patient  
286 anchor specific to functional walking capacity. Our work is thus complementary, as walking  
287 tests and quality of life questionnaires measure different constructs <sup>46</sup>. Indeed, changes in  
288 walking performance should not be used to infer changes in health-related quality of life,  
289 irrespective of whether the MCID is achieved.

290 The MCID of 25 meters for the 6MWD identified in this study is similar to that  
291 recently reported by Holland et al. among patients with diffuse parenchymal lung disease <sup>47</sup>  
292 and COPD patients <sup>44</sup>. As in the latter study, we identified a threshold distance at which  
293 patients can identify clinical change using the ROC method, rather than using the average  
294 distance associated with clinical change in a group of patients. Using this cutoff, the positive  
295 predictive value was 0.9. This means that, when patients improve their 6MWD by 25 meters,  
296 there is a 90% chance that they will feel a real improvement in their walking performance.  
297 This was also associated with a specificity of 0.92, and a sensitivity of 0.55, meaning that  
298 when patients do perceive a clinical change, there is a 55% chance that their walking capacity  
299 has improved by more than 25 m.

300 Unlike the study of Holland et al. among COPD patients <sup>44</sup>, we did not find a  
301 difference in the absolute change in 6MWD depending on the baseline walking distance. This  
302 might be due to the difference in the sample, as our patients were younger, and showed a  
303 higher baseline performance with less variability. This could also be due to the different  
304 nature of the disease itself.

305           The majority of patients achieved the estimated MCID after rehabilitation (93%). We  
306 chose to estimate the MCID between the 6th and 12th session, in order to avoid a skewed  
307 distribution of perceived change scores (figure 1), and to minimize recall bias. Thus, at this  
308 time, only 36% had achieved the MCID. This means that we had patients with change scores  
309 greater than the calculated MCID values who considered their walking capacity unchanged or  
310 worsened Conversely, other patients with change scores less than the calculated MCID  
311 considered their walking capacity improved (score  $\geq 2$ ). Moreover, there was no difference in  
312 maximal exercise capacity improvement between patients achieving MCID for the 6MWD  
313 between the 2<sup>nd</sup> and 3<sup>rd</sup> evaluation and those who did not. This seems logical, as the 6MWT  
314 remains a submaximal walk tests, and as the correlation between improvement in 6MWD and  
315 maximal exercise capacity improvement was moderate, as previously reported <sup>6</sup>. Our MCID  
316 values should thus be interpreted with caution, particularly when making judgments about  
317 individual patients, and exercise capacity assessment remains the gold standard for prognosis.

318           Studies of retrospective change have shown that subjects tend to judge their  
319 assessments of change based on their current condition, remembering backwards in time from  
320 that point rather than remembering their initial condition and working forward <sup>48</sup>. Thus,  
321 estimating perceived change every 6 to 8 sessions allowed us to minimize this bias, even  
322 though this methodology is not as strong as would be a prognostic study of predicted change.

323  
324           The estimation of the MCID for the 6MWD was different when determined by the  
325 patient or the physiotherapist. Previous studies in other diseases concerning agreement  
326 between patients' and clinicians' ratings of change showed inconsistent results, ranging from  
327 poor <sup>49, 50</sup> to good <sup>26</sup> agreement. Physicians may have a skewed perspective on functional  
328 change given the little time spent actually observing patients <sup>51</sup>. However, one could think  
329 that other health professionals, such as physiotherapists, who are more familiar with the day-  
330 to-day functioning of patients, would have an estimation of clinical change closer to that of

331 patients. This was not the case in our study, as there was poor agreement between change  
332 assessed by patients and that assessed by physiotherapists (Cohen  $\kappa$  correlation coefficient =  
333 0.17). For example, among patients who rated themselves  $<2$ , 16 were considered stable or  
334 worsened by the physiotherapist (score  $< 2$ ), and 23 were considered improved (score  $\geq 2$ ).  
335 However, there was no significant difference between these 2 groups for the 6MWD (table 4).  
336 Physiotherapists may take into account many subjective (general appearance of the patient,  
337 mood, other complaints, etc.) and objective data (total work on ergometers, HR during  
338 training sessions) in their judgment, related to their own experience and history. Some of  
339 these data were probably considered more important by the physiotherapist than by the  
340 patients in interpreting the perception of clinical change. However, in our study, there was no  
341 significant HR variation between the 2<sup>nd</sup> and the 3<sup>rd</sup> evaluation. This might not have affected  
342 the change perceived by the physiotherapist. Future studies may include regression analyses  
343 to identify the components of relevant clinical change for the therapist and the patient.

344 Our study failed to identify an MCID with satisfactory metrological qualities for the  
345 200MFWT. The anchor-based method did not show a significant difference in means between  
346 patients rating  $<2$  and those rating  $\geq 2$ . A 4.2-second improvement in the 200MFWTT was  
347 determined as the MCID when using the distribution method. However, this finding has to be  
348 interpreted very cautiously as the ROC method did not allow us to identify a threshold with  
349 sufficient metrological qualities for a time improvement at which patients can identify a  
350 clinical change. The 200MFWT test explores higher exercise intensities than does the 6MWT  
351 <sup>7</sup>. It could be harder for a patient to interpret his feelings during a test that is closer to his  
352 maximal capacity. Indeed, the 6MWT is submaximal moderate exercise, approximately  
353 corresponding to the first VT <sup>6, 52</sup>. Thus, it might be easier for patients to have a better  
354 perception of their walking ability during this test, which may better reflect their daily  
355 activities than the 200MFWT, which is more like running to catch a bus, for example. The



356 200WFWT might be more useful as a tool to help design or assess high intensity  
357 rehabilitation programs, such as interval training.

358         The sensitivity and specificity of tests are often used to choose a cutoff for the  
359 significance of a clinical or biological variable. Here, we chose the PPV and NPV to identify  
360 a meaningful cutoff for the MCID. Indeed, we chose these metrologic properties to find  
361 answers to the question raised: will a patient who improves beyond the identified MCID  
362 perceive a clinical change? Based on our results, with a 25-meter cutoff, we can affirm that in  
363 this population, 90% of patients who improved their 6MWD by more than 25 meters  
364 perceived a meaningful clinical change in their walking ability. Conversely, among patients  
365 who improved by less than 25 meters, 66% did not perceive any change. The PPV is  
366 influenced by the prevalence of the studied parameter in the population considered. However,  
367 the anthropometric characteristics and baseline walk performance of our sample was quite  
368 similar to that of other studies in the field <sup>7,9</sup>.

369         By defining the threshold for clinically important change, we improve our ability to  
370 interpret the effects of cardiac rehabilitation programs in routine clinical practice as well as in  
371 randomized clinical trials that assess the effectiveness of interventions. Thus, an MCID  
372 reference improvement of 25 meters for the 6MWD could serve as an explicit therapeutic goal  
373 for rehabilitation or other therapeutic interventions that aim to improve walking ability and  
374 participation levels for CAD patients. Indeed, a valid MCID for 6MWD improvement is  
375 useful for the clinical interpretation of individual rehabilitation programs, but also the clinical  
376 significance of intervention studies that may find statistical improvements in 6MWD but may  
377 not achieve a clinically meaningful threshold. Moreover, sample size heavily influences the  
378 statistical significance of an improvement in performance in a clinical trial. The clinically  
379 interpretable effects of a training program on measurements of performance can be examined  
380 according to standards of meaningful change by comparing the proportion of treatment and

381 control groups who achieve change and calculating the number needed to treat <sup>53</sup>. Finally,  
382 sample size estimates are needed in the planning stage of research studies and should be based  
383 on the ability to detect clinically significant levels of change.

384

385

### 386 **Study Limitations**

387 Our study in one cardiac rehabilitation department comprised a relatively small sample  
388 of stable CAD patients and included very few women. Moreover, they all benefited from  
389 standardized care during the acute phase, which may vary from one cardiology acute care  
390 department to another. Thus, we cannot generalize our results to the whole population of  
391 CAD patients. Future studies with larger sample sizes including patients with different  
392 functional statuses are now needed to refine our estimates and to determine how MCID values  
393 are affected by time since the MI, by the severity and/or clinical features of the initial MI, and  
394 by the initial acute care procedure.

395 Even though we chose to assess the MCID at the period with the widest diversity in  
396 degrees of self-perceived change, very few patients (4) reported a decline in walking ability.  
397 This seems logical, given the well-known benefits of cardiac rehabilitation programs. Among  
398 these 4 patients, only one really had a lower 6MWD (-5 meters). We were therefore unable to  
399 assess whether the MCID for decline differed from the MCID for improvement, as has  
400 previously been reported <sup>54</sup>.

401 Finally, only a small number of physical therapists participated in the  
402 assessment of change, and all of these had specialized in cardiac rehabilitation. Future studies  
403 should include more physiotherapists from multiple settings.

404

405 **CONCLUSIONS**

406 Our study provides the first estimates of a minimal clinically important difference,  
407 approximately 25 meters, in performance at the 6-minute walk test in a CAD population. This  
408 result supports the use of the 6-MWT during cardiac rehabilitation programs in CAD patients  
409 after ACS , and will help practitioners and researchers interpret changes in the 6MWD in this  
410 population.

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