

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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► **To cite this version:**

Vincent Gremeaux, Odile Troisgros, Sylvie Benaïm, Armelle Hannequin, Yves Laurent, et al.. 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.. Archives of Physical Medicine and Rehabilitation, WB Saunders, 2011, 92 (4), pp.611-9. 10.1016/j.apmr.2010.11.023 . hal-00702219

HAL Id: hal-00702219

<https://hal-univ-bourgogne.archives-ouvertes.fr/hal-00702219>

Submitted on 4 Jun 2012

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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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15
16 Walk tests are often used in the assessment of functional capacity in patients with
17 pulmonary and cardiac diseases ¹. They require less technical expertise than laboratory tests ²,
18 are inexpensive and easy to administer, and employ an activity that individuals perform on a
19 daily basis, *i.e.* walking ³. The 6-Minute Walk Test (6MWT) is the most validated field test in
20 cardiorespiratory diseases ⁴, 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) ^{2,5} and with CAD ⁶. Recent data showed that, in CAD patients, this test is submaximal

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

26 The 200-Meter Fast Walk Test (200MFWT) has recently been developed in healthy
27 elderly people and in CAD patients ^{7, 11}. It has also been used to assess improvements in
28 functional capacity after a training program in elderly ¹² and CAD patients ⁷. 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 ^{13, 14}.

33 Field walk tests are objective measures that provide a means to monitor response to
34 treatment ³. 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” ¹⁵. The MCID is different from the Minimal Detectable Change, that
43 indicates the amount of change required to exceed measurement variability ^{16, 17}. 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 ^{16, 18}. 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 ¹⁹.
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 ^{15, 16, 20-23}. They are
56 usually divided into 2 categories: distribution-based and Anchor-based ²¹.

57 Anchor-based methods involve comparing a patient’s change score with another
58 measure of clinically relevant change ²⁴. 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 ^{16, 25}(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 ²⁶. 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 ²⁷.

66 Distribution-based methods, such as the standard error of the measure (SEM) ²⁸ and
67 the effect size ²⁹, 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 ³⁰.

70 There is as yet no accepted threshold for clinically significant change in cardiac
71 diseases in the 6MWT walked distance (6MWD)³¹, 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 recommendations³² (i.e. β -
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 criteria³³, (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 protocol³⁴, before entering the rehabilitation programme
102⁴¹, and individualized on the basis of preliminary physical activity habits, determined using
103 the Dijon physical activity score questionnaire¹¹. 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 formula³⁵ as follows: training HR = rest HR + 75% (max HR
106 – rest HR). During training sessions, Borg scale with level 6 to 20 was also used³⁶. The
107 target was set between 13 and 15.

108 - Individual and group educational interventions based on the patient's risk factors³⁷.

109 The training program was in line with the latest recommendations in the field³⁷⁻³⁹,
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 6th and 12th 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 ¹⁵.

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 test⁴⁰.

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^{7, 11}.

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 ≥ 2) from those who did not (score <2). As previously
155 described, the mean score change for the smallest meaningful change (*i.e.* ≥ 2) was taken as
156 the MCID for both walk tests^{41, 42}. 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 σ_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 MCID²⁸. The
171 intraclass correlation coefficients used for test-retest reliability were calculated from data of a
172 previous study⁷, 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 κ 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 association⁴³.

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^{41, 42, 44}, 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 ± 56.5 meters in the 6MWD ($15.7 \pm$
199 12.2%), and of 5 ± 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 ± 0.8 and 16 ± 0.9 before, and 14.6 ± 0.9 and 16.1 ± 1 after,
204 respectively. All patients significantly improved maximal exercise capacity from 7.2 ± 1.7
205 METS at baseline to 9 ± 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 ± 13.8 and
207 126.4 ± 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 2nd and 3rd 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 2nd evaluation, as well as between the 2nd
216 and the 3rd, and the 3rd and the final evaluation, are shown in figure 2. The distribution was
217 best balanced between the 2nd and 3rd evaluation. We thus considered that this period of the
218 rehabilitation program (between the 6th and 12th 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 2nd and 3rd evaluation.

221 At this time, 40 patients rated themselves as ≥ 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 ≥ 2 and 21 rated < 2 .
239 The mean change in the 6MWD in the patients classified as improved by the physiotherapist
240 (≥ 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 κ 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 ≥ 2)

258 (table). There was no significant difference between patients classified <2 and those classified
259 ≥ 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 2nd and 3rd 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 ± 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 ⁴⁵. 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 ⁴⁶. 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 ⁴⁷
292 and COPD patients ⁴⁴. 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 ⁴⁴, 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 ≥ 2). Moreover, there was no difference in
312 maximal exercise capacity improvement between patients achieving MCID for the 6MWD
313 between the 2nd and 3rd 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 ⁶. 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 ⁴⁸. 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 ^{49, 50} to good ²⁶ agreement. Physicians may have a skewed perspective on functional
328 change given the little time spent actually observing patients ⁵¹. 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 κ 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 ≥ 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 2nd and the 3rd 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 ≥ 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 ⁷. 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 ^{6, 52}. 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 ^{7,9}.

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 ⁵³. 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 ⁵⁴.

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.

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CONCLUSIONS

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

Acknowledgments: The authors would like to thank the whole rehabilitation team for their participation in this study. We would also like to thank Dr Dupeyron and Gelis for their unconditional 10-years support. The English was revised by Philip Bastable.

- 421 1. Guyatt GH, Thompson PJ, Berman LB, Sullivan MJ, Townsend M, Jones NL et al.
422 How should we measure function in patients with chronic heart and lung disease? *J Chronic*
423 *Dis* 1985;38(6):517-24.
- 424 2. Lipkin DP, Scriven AJ, Crake T, Poole-Wilson PA. Six minute walking test for
425 assessing exercise capacity in chronic heart failure. *Br Med J (Clin Res Ed)*
426 1986;292(6521):653-5.
- 427 3. Singh S. The use of field walking tests for assessment of functional capacity in
428 patients with chronic airways obstruction. *Physiotherapy* 1992;78:102-4.
- 429 4. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the
430 measurement properties of functional walk tests used in the cardiorespiratory domain. *Chest*
431 2001;119(1):256-70.
- 432 5. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW et al. The
433 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can*
434 *Med Assoc J* 1985;132(8):919-23.
- 435 6. Gayda M, Temfemo A, Choquet D, Ahmaidi S. Cardiorespiratory requirements and
436 reproducibility of the six-minute walk test in elderly patients with coronary artery disease.
437 *Arch Phys Med Rehabil* 2004;85(9):1538-43.
- 438 7. Gremeaux V, Deley G, Duclay J, Antoine D, Hannequin A, Casillas JM. The 200-m
439 fast-walk test compared with the 6-min walk test and the maximal cardiopulmonary test: a
440 pilot study. *Am J Phys Med Rehabil* 2009;88(7):571-8.
- 441 8. Nogueira PA, Leal AC, Pulz C, Nogueira ID, Filho JA. Clinical reliability of the 6
442 minute corridor walk test performed within a week of a myocardial infarction. *Int Heart J*
443 2006;47(4):533-40.
- 444 9. Verrill DE, Barton C, Beasley W, Lippard M, King CN. Six-minute walk performance
445 and quality of life comparisons in North Carolina cardiac rehabilitation programs. *Heart Lung*
446 2003;32(1):41-51.
- 447 10. O'Keeffe ST, Lye M, Donnellan C, Carmichael DN. Reproducibility and
448 responsiveness of quality of life assessment and six minute walk test in elderly heart failure
449 patients. *Heart* 1998;80(4):377-82.
- 450 11. Gremeaux V, Iskandar M, Kervio G, Deley G, Perennou D, Casillas JM. Comparative
451 analysis of oxygen uptake in elderly subjects performing two walk tests: the six-minute walk
452 test and the 200-m fast walk test. *Clin Rehabil* 2008;22(2):162-8.
- 453 12. Deley G, Kervio G, Van Hoecke J, Verges B, Grassi B, Casillas JM. Effects of a one-
454 year exercise training program in adults over 70 years old: a study with a control group.
455 *Aging Clin Exp Res* 2007;19(4):310-5.
- 456 13. Rognmo O, Hetland E, Helgerud J, Hoff J, Slordahl SA. High intensity aerobic
457 interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in
458 patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil* 2004;11(3):216-22.
- 459 14. Swain DP, Franklin BA. Comparison of cardioprotective benefits of vigorous versus
460 moderate intensity aerobic exercise. *Am J Cardiol* 2006;97(1):141-7.
- 461 15. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the
462 minimal clinically important difference. *Control Clin Trials* 1989;10(4):407-15.
- 463 16. Beaton DE, Bombardier C, Katz JN, Wright JG, Wells G, Boers M et al. Looking for
464 important change/differences in studies of responsiveness. OMERACT MCID Working
465 Group. Outcome Measures in Rheumatology. Minimal Clinically Important Difference. *J*
466 *Rheumatol* 2001;28(2):400-5.

- 467 17. de Vet HC, Terwee CB, Ostelo RW, Beckerman H, Knol DL, Bouter LM. Minimal
468 changes in health status questionnaires: distinction between minimally detectable change and
469 minimally important change. *Health Qual Life Outcomes* 2006;4:54.
- 470 18. Hays RD, Woolley JM. The concept of clinically meaningful difference in health-
471 related quality-of-life research. How meaningful is it? *Pharmacoeconomics* 2000;18(5):419-
472 23.
- 473 19. Wells G, Beaton D, Shea B, Boers M, Simon L, Strand V et al. Minimal clinically
474 important differences: review of methods. *J Rheumatol* 2001;28(2):406-12.
- 475 20. Jacobson N, Follette W, Revenstorf D. Toward a standard definition of clinically
476 significant change. *Behav Ther* 1986;17:308-11.
- 477 21. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in
478 health-related quality of life. *J Clin Epidemiol* 2003;56(5):395-407.
- 479 22. Crosby RD, Kolotkin RL, Williams GR. An integrated method to determine
480 meaningful changes in health-related quality of life. *J Clin Epidemiol* 2004;57(11):1153-60.
- 481 23. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining
482 meaningful change in psychotherapy research. *J Consult Clin Psychol* 1991;59(1):12-9.
- 483 24. Deyo RA, Diehr P, Patrick DL. Reproducibility and responsiveness of health status
484 measures. Statistics and strategies for evaluation. *Control Clin Trials* 1991;12(4 Suppl):142S-
485 58S.
- 486 25. Deyo RA, Centor RM. Assessing the responsiveness of functional scales to clinical
487 change: an analogy to diagnostic test performance. *J Chronic Dis* 1986;39(11):897-906.
- 488 26. Stratford PW, Binkley FM, Riddle DL. Health status measures: strategies and analytic
489 methods for assessing change scores. *Phys Ther* 1996;76(10):1109-23.
- 490 27. Beaton DE. Understanding the relevance of measured change through studies of
491 responsiveness. *Spine* 2000;25(24):3192-9.
- 492 28. Wyrwich KW, Nienaber NA, Tierney WM, Wolinsky FD. Linking clinical relevance
493 and statistical significance in evaluating intra-individual changes in health-related quality of
494 life. *Med Care* 1999;37(5):469-78.
- 495 29. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health
496 status. *Med Care* 1989;27(3 Suppl):S178-89.
- 497 30. Beaton DE, Boers M, Wells GA. Many faces of the minimal clinically important
498 difference (MCID): a literature review and directions for future research. *Curr Opin*
499 *Rheumatol* 2002;14(2):109-14.
- 500 31. Pollentier B, Irons SL, Benedetto CM, Dibenedetto AM, Loton D, Seyler RD et al.
501 Examination of the six minute walk test to determine functional capacity in people with
502 chronic heart failure: a systematic review. *Cardiopulm Phys Ther J* 2010;21(1):13-21.
- 503 32. Smith SC, Jr., Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC et al.
504 AHA/ACC guidelines for secondary prevention for patients with coronary and other
505 atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and
506 Blood Institute. *Circulation* 2006;113(19):2363-72.
- 507 33. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of
508 congestive heart failure: the Framingham study. *N Engl J Med* 1971;285(26):1441-6.
- 509 34. Bruce RA. Exercise testing of patients with coronary heart disease. Principles and
510 normal standards for evaluation. *Ann Clin Res* 1971;3(6):323-32.
- 511 35. Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate; a
512 longitudinal study. *Ann Med Exp Biol Fenn* 1957;35(3):307-15.
- 513 36. Borg G, Linderholm H. Exercise performance and perceived exertion in patients with
514 coronary insufficiency, arterial hypertension and vasoregulatory asthenia. *Acta Med Scand*
515 1970;187(1-2):17-26.

- 516 37. Monpère C, Sellier P, Meurin P, Aeberhard P, D'Agrosa Boiteux M, Iliou M et al.
517 Recommendations of the French Society of Cardiology concerning cardiac rehabilitation,
518 Version 2. *Arch Mal Coeur Vaiss* 2002;95:962-97.
- 519 38. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JA et al. Core
520 components of cardiac rehabilitation/secondary prevention programs: 2007 update: a
521 scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation,
522 and Prevention Committee, the Council on Clinical Cardiology; the Councils on
523 Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and
524 Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation.
525 *J Cardiopulm Rehabil Prev* 2007;27(3):121-9.
- 526 39. Bjarnason-Wehrens B, Mayer-Berger W, Meister ER, Baum K, Hambrecht R, Gielen
527 S. Recommendations for resistance exercise in cardiac rehabilitation. Recommendations of
528 the German Federation for Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc*
529 *Prev Rehabil* 2004;11(4):352-61.
- 530 40. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*
531 2002;166(1):111-7.
- 532 41. Beninato M, Gill-Body KM, Salles S, Stark PC, Black-Schaffer RM, Stein J.
533 Determination of the minimal clinically important difference in the FIM instrument in
534 patients with stroke. *Arch Phys Med Rehabil* 2006;87(1):32-9.
- 535 42. Lang CE, Edwards DF, Birkenmeier RL, Dromerick AW. Estimating minimal
536 clinically important differences of upper-extremity measures early after stroke. *Arch Phys*
537 *Med Rehabil* 2008;89(9):1693-700.
- 538 43. Cohen J. *Statistical power analysis for the behavioural sciences*. New York: Academic
539 Pr; 1977.
- 540 44. Holland AE, Hill CJ, Rasekaba T, Lee A, Naughton MT, McDonald CF. Updating the
541 minimal important difference for six-minute walk distance in patients with chronic
542 obstructive pulmonary disease. *Arch Phys Med Rehabil* 2010;91(2):221-5.
- 543 45. Wyrwich KW, Spertus JA, Kroenke K, Tierney WM, Babu AN, Wolinsky FD.
544 Clinically important differences in health status for patients with heart disease: an expert
545 consensus panel report. *Am Heart J* 2004;147(4):615-22.
- 546 46. McDowell I, McDowell C. *Measuring health: a guide to rating scales and*
547 *questionnaires*. University of Ottawa: Oxford university press; 1987.
- 548 47. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Small changes in six-
549 minute walk distance are important in diffuse parenchymal lung disease. *Respir Med*
550 2009;103(10):1430-5.
- 551 48. Ross M. Relationship of implicit theories to the construction of
552 personal histories. *Psychol Rev* 1989;96:341-57.
- 553 49. Kwok CK, O'Connor GT, Regan-Smith MG, Olmstead EM, Brown LA, Burnett JB et
554 al. Concordance between clinician and patient assessment of physical and mental health
555 status. *J Rheumatol* 1992;19(7):1031-7.
- 556 50. Slevin ML, Plant H, Lynch D, Drinkwater J, Gregory WM. Who should measure
557 quality of life, the doctor or the patient? *Br J Cancer* 1988;57(1):109-12.
- 558 51. Wolfe F, Pincus T. Listening to the patient: a practical guide to self-report
559 questionnaires in clinical care. *Arthritis Rheum* 1999;42(9):1797-808.
- 560 52. Noonan V, Dean E. Submaximal exercise testing: clinical application and
561 interpretation. *Phys Ther* 2000;80(8):782-807.
- 562 53. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the
563 clinical significance of health status measures. *Mayo Clin Proc* 2002;77(4):371-83.

564 54. Schwartz AL, Meek PM, Nail LM, Fargo J, Lundquist M, Donofrio M et al.
565 Measurement of fatigue. determining minimally important clinical differences. J Clin
566 Epidemiol 2002;55(3):239-44.
567
568