occurred 2 years after a relatively short (6 months) period of ponatinib treat-
ment. These dynamics raise concerns that certain BCR/ABL1 kinase inhibitors may induce a vascular disease process that continues even after discontinua-
tion of the drug. Furthermore, this vascular disease process may involve multiple vascular territories. Yet, the very nature and mechanisms of this vascular disease process remain to be defined. A previous report of a patient with a cerebrovascular presentation while receiving treatment with ponatinib after nilotinib illustrated an intra-
cranial artery disease pattern that resembled Moya Moya disease and raised concern for vasculitis.6 At aut-
topsy, however, there was no evidence for vasculitis, and the degree of atherosclerosis was only mild. Con-
cerns for vasculitis were also raised in the current case, but related studies yielded negative results, at least at the time of evaluation. Although vaso-
spasm might have contributed to the acute coronary presentation, the pres-
cence of collateral vessels on lower extremity angiography indicates the presence of a more chronic “peripheral occlusive arterial disease” process. The exact timeline of such a process, however, remains undefined, as does the impact of serial surveillance ankle-brachial indices.

Conclusion. This case illustrates very well the need for long-term and comprehensive cardiovascular moni-
toring of patients treated with BCR/ABL1 kinase inhibitors. It also points out the potential merit of assessing traditional and genetic risk markers for atheroscle-
rosis. For instance, the factor V Leiden sequence variation, for which the pa-
tient was heterozygous, has been found in experimental models to lead not only to venous and arterial thrombotic events but also to progressive atherosclerosis, which can be considerably reduced by atorvastatin and almost completely eliminated by the combination of atorvastatin with amlodipine.7,8 Although it remains purely speculative whether this genetic variant contributed to the presentation of this patient, the interaction between coagulation and atherogenesis is certainly intriguing, as are the parallels in the scope of vascular events in these studies with ponatinib in clinical practice.

SUPPLEMENTAL ONLINE MATERIAL
Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Joerg Herrmann, MD
Malcolm R. Bell, MD
Rebekkah L. Warren, MD, PhD
Amir Lerman, MD
Mark D. Fleming, MD
Minral Patnaik, MBBS
Mayo Clinic
Rochester, Minnesota

5. Vallet P, Hadziyusufovic E, Schermthaner GH, Wolf D, Ras D, le Coutre P. Vascular safety issues in CML patients treated with BCR/ABL1 kinase inhibi-
8. Trion A, de Maat M, Jukema W, et al. Anti-atherosclerotic effect of amlodipine, alone and in combi-

http://dx.doi.org/10.1016/j.mayocp.2015.05.013

Accumulated Short Bouts of Physical Activity Are Associated With Reduced Premature All-Cause Mortality: Implications for Physician Promotion of Physical Activity and Revision of Current US Government Physical Activity Guidelines

To the Editor: Current physical activity (PA) guidelines issued by the US Department of Health and Human Ser-
dinces recommend that adults engage in 150 min/wk or more of moderate to vigorous PA (MVPA). Stated in the guidelines, this dose of MVPA is to occur in bouts lasting at least 10 min-
utes; thus, a brisk 6-minute MVPA walk from the car to the office would not count toward the 150 min/wk goal.

Current discussion has been raised about whether this “bou"t restriction” in the government MVPA guidelines should be lifted/modiﬁed. This discussion stems from emerging research revealing that accumulation of non-
bout MVPA (MVPA accumulating in <10-minute bouts) is favorably associ-
ed with numerous health outcomes (eg, C-reactive protein level).1 No study, however, has compared non-
bout and bout MVPA accumulation with regard to mortality risk, which was this study’s purpose.

Data from the population-based 2003-2006 National Health and Nutrition Examination Survey were used, with these data linked to death certiﬁcates from the National Death Index; person-months of follow-up were calculated from the date of the interview until death or censoring on December 31, 2011, whichever came first.

Physical activity was assessed using an ActiGraph model 7164 accelerom-
eter; activity counts per minute of 2020 or more deﬁned MVPA, with those having at least 4 days of 10 h/d or more of monitoring included in the analyses. Bout (≥10 minutes) and nonbout
(<10 minutes) MVPA were evaluated. A 10-minute bout was defined as 10 or more consecutive minutes above the MVPA cut point. Nonbout MVPA was calculated as bout MVPA subtracted from total MVPA (ie, nonbout MVPA = total MVPA − bout MVPA).

A total of 5834 adults (aged 20-85 years; mean age, 46.5 years) provided complete data. The mean follow-up was 80.7 months (range, 0-107 months), and 550 participants died during this period. The weighted mean (SE) minutes per day of nonbout and bout MVPA was 17.3 min/d (0.3 min/d) and 6.7 min/d (0.3 min/d), respectively. Compared with those alive at follow-up, those who died engaged in less nonbout MVPA at baseline (7.0 min/d vs 2.1 min/d for those who died; P<.05) and bout MVPA (hazard ratio, 0.73; P=.02) and bout MVPA (hazard ratio, 0.83; P=.05) were associated with decreased all-cause mortality (Table); the Harrell C concordance statistic was 0.86, and the proportional hazards assumption was not violated (P=.14).

In this study, both nonbout and bout MVPA were independently associated with decreased all-cause mortality, underscoring the promotion of both nonbout and bout MVPA. In addition to the nonbout MVPA-mortality relationship observed in this study, other studies have found that nonbout PA can increase cardiorespiratory fitness and promote weight loss.2,3 Further, nonbout MVPA may help to minimize prolonged sedentary behavior, which has emerged as an independent indicator of health status. The observed findings have implications for future revisions of the MVPA guideline, and from a clinical perspective, these findings underscore the importance of physicians not only recommending bout-based MVPA per the US Department of Health and Human Services guidelines but also promoting nonbout MVPA to their patients.

### TABLE. Associations of Bout and Nonbout MVPA With Decreased All-Cause Mortality in 5834 Participants in the 2003-2006 NHANES

<table>
<thead>
<tr>
<th>MVPAa</th>
<th>Cox proportional hazards ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonbout, 10-min/d increase</td>
<td>0.73</td>
<td>0.57-0.95</td>
<td>.02</td>
</tr>
<tr>
<td>Bout, 10-min/d increase</td>
<td>0.83</td>
<td>0.70-0.99</td>
<td>.05</td>
</tr>
<tr>
<td>Covariates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, 1-y increase</td>
<td>1.08</td>
<td>1.07-1.10</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female vs male</td>
<td>0.56</td>
<td>0.45-0.71</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other vs white</td>
<td>1.07</td>
<td>0.83-1.35</td>
<td>.58</td>
</tr>
<tr>
<td>Nonsmoker vs smoker</td>
<td>0.47</td>
<td>0.36-0.61</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI, 1-kg/m² increase</td>
<td>1.00</td>
<td>0.97-1.02</td>
<td>.96</td>
</tr>
<tr>
<td>Some college vs less education</td>
<td>0.77</td>
<td>0.60-0.99</td>
<td>.04</td>
</tr>
<tr>
<td>CRP, 1-mg/dL increase</td>
<td>1.18</td>
<td>1.10-1.26</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CAD vs no CAD</td>
<td>1.47</td>
<td>1.03-2.10</td>
<td>.03</td>
</tr>
</tbody>
</table>

1BMI = body mass index; CAD = physician-diagnosed coronary artery disease; CRP = C-reactive protein; MVPA = moderate to vigorous physical activity; NHANES = National Health and Nutrition Examination Survey.

2Nonbout MVPA was defined as MVPA accumulated in less than 10-minute intervals/bouts; bout MVPA was defined as MVPA accumulated in 10-minute or more intervals/bouts.

3C conversion factor: To convert CRP value to nmol/L, multiply by 9.524.

In the Medical Images entitled “Multiple Painful Nodules and Uterine Leiomyomas” published in the March 2015 issue of Mayo Clinic Proceedings (Mayo Clin Proc. 2015;90(3):423-424), the first author’s name was incorrect; it should have been listed as Pablo Fernández-Crehuet.

http://dx.doi.org/10.1016/j.mayocp.2015.07.001


http://dx.doi.org/10.1016/j.mayocp.2015.07.002