Depression is associated with worse patency and recurrent leg symptoms after lower extremity revascularization

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Objectives: Depression is associated with worse outcomes after coronary artery bypass surgery, but its association with the results after revascularization for symptomatic peripheral arterial disease (PAD) is unknown. This study assessed the association between depression and patency, recurrent symptoms, and limb salvage after revascularization for symptomatic PAD.

Methods: Electronic medical records were retrospectively reviewed for all patients with symptomatic PAD who underwent intervention (open, endovascular, or combined) between January 2000 and October 2004. All patients were previously screened for depression, and treatment was initiated as indicated by the primary care physician or psychiatrist. Demographic data and outcomes were recorded using published guidelines. Outcomes of interest included primary patency of the revascularization (bypass graft or angioplasty/stented artery), assisted primary patency, secondary patency, recurrent symptomatic ipsilateral PAD, and major amputation. Follow-up was available for all patients (mean, 23.4 ± 14.1 months).

Results: Board-certified vascular surgeons performed all interventions. At the time of intervention, 78 (36.1%) of 216 patients had been diagnosed with depression. Compared with those without depression, depressed patients were younger (64.4 vs 69.1 years; \( P = .001 \)), currently using tobacco (74.4% vs 51.4%; \( P = .001 \)), and less likely to have hypertension (79.5% vs 89.9%; \( P = .03 \)). No other significant differences were noted for cardiovascular risk factors or prevalent comorbidities. During follow-up, 50 patients (23.1%) had failing or failed revascularizations, and 24 (11%) had amputations. Those with depression at the time of the PAD intervention, compared at 24 months with patients without depression, had significantly worse primary patency (58.2% vs 79.8%; \( P = .02 \)), primary assisted patency (59.5% vs 81.5%; \( P = .01 \)), and secondary patency (60.2% vs 82.2%; \( P = .007 \)). They also had a significantly increased risk of recurrent symptomatic PAD (33.7% vs 20.8%; \( P = .03 \)) but not major amputation (13.8% vs 10.4%; \( P = .73 \)). By multivariate analysis, patients with depression were at significantly increased risk for recurrent symptomatic PAD (hazard ratio [HR], 1.77; 95% confidence interval [CI], 1.03 to 3.02; \( P = .04 \)) and failure of revascularization (HR, 2.18; 95% CI, 1.22 to 3.88; \( P < .01 \)), but not major amputation.

Conclusions: Depression is common among patients undergoing intervention for symptomatic PAD. After intervention, patients with depression have worse outcomes for the affected leg. Prospective analysis is required to confirm these results.

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sion in this report. Approval for this project was obtained from the Institutional Review Board for Human Subjects Research at the Western New York VA Hospital.

Excluded from the study were three patients who were unable to complete the depression evaluation because of severe dementia (n = 2) and chronic schizophrenia and aphasia (n = 1). Thus, 216 patients met the inclusion criteria (symptomatic atherosclerotic occlusive PAD, ability to complete a depression evaluation) and formed the basis of this report. A retrospective electronic medical record review was completed for all patients. Preoperative variables, periprocedural results, and long-term outcome data were gathered using recommended reporting standards. Follow-up data were available for all patients (mean 23.4 ± 14.1 months).

For this study, depression was defined as significant depressive symptoms resulting in a recommendation for treatment with antidepressant medication or psychosocial therapy, or both. Depression was diagnosed by the primary care provider or a psychiatrist before the decision was made to intervene for symptomatic PAD. Because depression is frequently underdiagnosed and undertreated, VA protocol mandates that all patients should be screened for depression using a two-part protocol. The initial evaluation was performed using the General Health Questionnaire—12, a screening tool with good reliability and validity that is widely used in primary care. A score of >3 resulted in further evaluation by the patient’s primary health care provider before the diagnosis of depression was made. This depression screening is repeated annually.

Board-certified vascular surgeons performed all interventions. The indications for revascularization included disabling claudication in 62 patients (28.7%), ischemic rest pain in 48 (22.2%), and tissue loss in 106 (49.1%). Interventions included open surgery in 123 patients (56.9%), percutaneous revascularization in 68 (31.5%), and combined open/endovascular procedures in 25 (11.6%).

After revascularization, patients were examined at 3 months, and then at 6-month intervals for clinical assessment, which included femoral and distal pulses and recurrence of ipsilateral symptoms, and a vascular laboratory examination, which included ankle-brachial index (ABI) measurements, graft or stent velocities, and duplex imaging. At each examination, patients were queried about incident PAD events, including care received at private-sector hospitals.

The vascular laboratory studies were reviewed for all patients to confirm the patency of the revascularization. Angiography and repeat intervention were performed when clinically indicated. Patients who missed vascular clinic appointments were contacted by phone to ascertain clinical status and reschedule follow-up visits.

The primary outcome was primary patency of the bypass graft or endovascular reconstruction, and secondary outcomes included primary assisted patency, secondary patency, and major amputation. These outcomes were defined using accepted standards. Finally, recurrent symptoms in the revascularized leg were assessed as a marker of long-term clinical success, an outcome used in other vascular territories. Relief of symptoms is an important goal for both the patient and clinician and does not necessarily correlate with patency: some patients have an asymptomatic graft occlusion and others have recurrent symptoms owing to progression of PAD in another vascular bed. The diagnosis of recurrent symptoms was defined as initial relief of symptoms with subsequent recurrence based on patient history (claudication, rest pain, or tissue loss) and confirmed by a physical examination showing a change in peripheral pulse results, presence of ulceration or gangrene, or a vascular laboratory study showing a reduction of ABI of ≥0.10 from maximum postprocedural value or graft occlusion, or both. To verify the distinction between vascular and nonvascular causes of symptoms, the relationship between symptoms and PAD was confirmed by arteriogram revealing new atherosclerotic occlusive lesions or graft occlusion, or intraoperative findings of graft occlusion.

The statistical analysis was conducted with SAS 9.1 software (SAS Institute, Cary, NC). Patients’ baseline characteristics were reported using descriptive statistics. For patients with and without depression, the demographics, comorbid illnesses, and clinical signs/symptoms were compared using χ² test for categoric variables and the Student t test for continuous variables. The log rank test was used to evaluate the association between depression and the outcomes after intervention.

Univariate and multivariate analysis were used to assess the relationship between preoperative factors and outcomes of interest. The variables included were age, depression, previous cardiac disease, previous lower extremity revascularization, prior carotid endarterectomy, prior CABG surgery, prior percutaneous coronary intervention, diabetes, tobacco use ever, current tobacco use or ≤1 year, hypertension, dyslipidemia, current statin use, carotid disease, renal disease, pulmonary disease, cerebrovascular disease, site of intervention (aortoiliac, femoropopliteal, femorotibial), indication for intervention (disabling claudication, rest pain, tissue loss), and type of intervention (endovascular, open, hybrid). The relative risk for these variables on the selected outcomes was estimated using the Cox proportional hazard model with adjustment for other confounders that may effect the outcome. All P values are reported as two-sided with significant α level = 0.05.

RESULTS

During the study period, 216 patients (99.5% men) underwent intervention for symptomatic PAD. Their mean age was 67.4 ± 10.5 years (range, 41.0 to 89.3 years), and 87.5% were white, 11.6% were African American, and 1% was Hispanic. At the time of intervention, 78 patients (36.1%) had been previously diagnosed with depression, and 58 were receiving antidepressant medications (74.4%), 2 (2.6%) were treated with only psychosocial counseling, and 18 (23.1%) refused treatment for depression. The small number of patients in each group precluded subgroup
Table I. Demographics and comorbid illnesses for patients undergoing intervention for symptomatic peripheral arterial disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Depressed (%)</th>
<th>Nondepressed (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.4</td>
<td>69.1</td>
<td>.001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>92.3</td>
<td>84.8</td>
<td>.30</td>
</tr>
<tr>
<td>African American</td>
<td>7.7</td>
<td>13.8</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>44.9</td>
<td>52.2</td>
<td>.30</td>
</tr>
<tr>
<td>Hypertension</td>
<td>79.5</td>
<td>89.9</td>
<td>.03</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>59</td>
<td>64.5</td>
<td>.42</td>
</tr>
<tr>
<td>Statin use</td>
<td>50.0</td>
<td>57.2</td>
<td>.31</td>
</tr>
<tr>
<td>Tobacco use</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ever</td>
<td>94.9</td>
<td>84.1</td>
<td>.02</td>
</tr>
<tr>
<td>≤1 year</td>
<td>74.4</td>
<td>51.4</td>
<td>.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>66.7</td>
<td>64.5</td>
<td>.75</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>29.5</td>
<td>36.2</td>
<td>.31</td>
</tr>
<tr>
<td>Previous procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>18.0</td>
<td>23.2</td>
<td>.37</td>
</tr>
<tr>
<td>CEA</td>
<td>9.0</td>
<td>9.4</td>
<td>.91</td>
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<tr>
<td>LE revascularization</td>
<td>23.8</td>
<td>21.7</td>
<td>.82</td>
</tr>
<tr>
<td>Contralateral amputation</td>
<td>5.1</td>
<td>5.1</td>
<td>.98</td>
</tr>
<tr>
<td>Renal disease</td>
<td>21.8</td>
<td>29.0</td>
<td>.21</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>26.9</td>
<td>53.6</td>
<td>.0001</td>
</tr>
</tbody>
</table>

CEA, Carotid endarterectomy; LE, lower extremity.

analysis based on the type of therapy, including refusal of treatment, or antidepressant medication.

At the time of intervention, the patient demographics, prevalent diseases, and prior vascular interventions were similar for patients with and without depression (Table I); however, patients with depression were significantly younger than nondepressed patients (64.4 ± 10.8 years vs 69.1 ± 9.9 years; P < .001). Patients with depression were less likely to require antihypertensive therapy (79.5% vs 89.9%; P = .03). Although depressed patients were more likely than nondepressed patients to have used tobacco within 1 year (74.4% vs 51.4%; P = .001) and during their lifetime (94.9% vs 84.1%; P = .02), they were less frequently diagnosed with pulmonary disease (26.9% vs 53.6%; P < .0001).

The indications for intervention, type of procedure, and site of vascular disease were similar for both groups of patients (Table II). Periprocedural outcomes were not significantly different for depressed patients compared with nondepressed patients for 30-day mortality (1.3% vs 5.1%; P = .16) or complications (17.9% vs 23.9%; P = .31). No differences were noted between depressed and nondepressed patients for ABI before intervention (0.40 ± 0.22 vs 0.37 ± 0.19; P = .30) and after intervention (0.82 ± 0.21 vs 0.85 ± 0.16; P = .22). The ABI for patients with depression rose from 0.40 ± 0.22 to 0.82 ± 0.21 (P < .0001) after revascularization and increased from 0.37 ± 0.19 to 0.85 ± 0.16 (P < .0001) for nondepressed patients.

Follow-up data were available for all patients, during which 50 patients (23.1%) had failing or failed revascularizations, 56 (25.9%) had recurrent symptomatic PAD, and 24 (11%) underwent major amputation. Of the 56 patients with recurrent symptoms, 18 (32.1%) had a patent reconstruction with progression of PAD in a separate vascular bed, and 38 (67.9%) had an associated loss of patency. Although 12 patients had failing or failed reconstructions (one patient with an asymptomatic failing graft and 11 patients with thrombosed revascularizations), they were not included in the analysis for recurrent symptoms because the events occurred before complete wound healing and were therefore not “recurrent.” During follow-up, no patients were noted to have PAD interventions at private-sector hospitals.

Table II. Summary of indications for intervention and operative management in 216 patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Depressed (%)</th>
<th>Nondepressed (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication for intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Claudication</td>
<td>23.1</td>
<td>31.1</td>
<td>.40</td>
</tr>
<tr>
<td>Rest pain</td>
<td>25.6</td>
<td>20.3</td>
<td></td>
</tr>
<tr>
<td>Tissue loss</td>
<td>50.0</td>
<td>49.3</td>
<td></td>
</tr>
<tr>
<td>Site of reconstruction*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortoiliac</td>
<td>42.3</td>
<td>52.1</td>
<td>.15</td>
</tr>
<tr>
<td>Femoropopliteal</td>
<td>42.3</td>
<td>27.5</td>
<td></td>
</tr>
<tr>
<td>Femorodistal</td>
<td>20.5</td>
<td>29.7</td>
<td></td>
</tr>
<tr>
<td>Type of reconstruction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open surgery</td>
<td>55.1</td>
<td>58.0</td>
<td>.88</td>
</tr>
<tr>
<td>Percutaneous procedure</td>
<td>32.1</td>
<td>31.2</td>
<td></td>
</tr>
<tr>
<td>Hybrid procedure</td>
<td>9.0</td>
<td>10.9</td>
<td></td>
</tr>
</tbody>
</table>

*Seventeen patients underwent combined aortoiliac and infrapopliteal reconstruction; therefore, the percentage of patients for each group is >100%.

Patients with depression at the time of revascularization had worse patency of the revascularization compared with those without depression. By product-limit estimate, patients with depression had significantly worse primary patency (24 months; 58.2% vs 79.8%; P = .02; Fig 1), primary assisted patency (24 months; 59.5% vs 81.5%; P = .01; Fig 2), and secondary patency (24 months; 60.2% vs 82.2%; P = .007; Fig 3).

With univariate analysis, factors significantly associated with worse primary patency rate included depression (hazard ratio [HR], 1.91; 95% confidence interval [CI], 1.10 to 3.38; P = .02), prior coronary artery disease events (HR, 2.00; 95% CI, 1.05 to 3.81; P = .04), aortoiliac vs femoropopliteal/femorotibial operation (HR, 0.374; 95% CI, 0.26 to 0.54; P < .0001), endovascular vs hybrid/open operation (HR, 0.58; 95% CI, 0.37 to 0.90; P = .02), and indication for operation (HR, 0.44; 95% CI, 0.22 to 0.90; P = .02).

By multivariate analysis, significant and independent predictors for failure of primary patency included depression (HR, 2.18; 95% CI, 1.22 to 3.88; P < .01), prior coronary artery disease events (HR, 2.11; 95% CI, 1.10 to 4.09; P = .03), femoropopliteal revascularization (HR, 2.63; 95% CI, 1.13 to 6.10; P = .03), and femorotibial revascularization (HR, 7.43; 95% CI, 3.33 to 16.59; P < .001). The results of multivariate analysis of predictors of
primary assisted and secondary patency were similar to those for primary patency (data not shown).

Depression was also associated with an increased risk for recurrent leg symptoms after revascularization. The product-limit estimate of time to recurrent symptoms was significantly worse for patients with depression at the time of intervention (24 months; 33.7% vs 20.8%; *P* = .03; Fig 4).

Univariate analysis showed that factors significantly associated with recurrent leg symptoms were depression (HR, 1.81; 95% CI, 1.06 to 3.08; *P* = .03), statin therapy (HR, 0.57; 95% CI, 0.34 to 0.97; *P* = .04), femorodistal revascularization (HR, 2.72; 95% CI, 1.40 to 5.28; *P* = .003), open/hybrid repair (HR, 4.13; 95% CI, 1.63 to 10.42; *P* = .003), and claudication (HR, 0.45; 95% CI,
0.22 to 0.90; \( P = .02 \)). By multivariate analysis, only depression significantly and independently predicted recurrent symptoms (HR, 1.77; 95% CI, 1.03 to 3.02; \( P = .04 \)), and claudication as an indication for intervention, compared with rest pain or tissue loss, was associated with decreased risk for recurrent symptoms (HR, 0.49; 95% CI, 0.26 to 0.92; \( P = .03 \)). When compared with nondepressed patients, depressed patients were not at increased risk for major amputation. The product-limit estimate of time to amputation was not significantly different between the two groups (24 months; 13.8% vs 10.4%; \( P = .73 \)).

**DISCUSSION**

Depression is associated with poorer outcomes for patients undergoing CABG; however, to our knowledge, no previous research has examined the influence of depression on outcomes after lower extremity revascularization. In the present study, 216 patients underwent intervention for symptomatic PAD. At the time of revascularization, 78 patients (36.1%) had been diagnosed with depression.

Depressed patients were younger and more likely to use tobacco but otherwise had similar atherosclerotic risk factors and comorbid conditions at the time of intervention. The two groups had similar indications for intervention, types of intervention, and periprocedural outcomes. Patients with depression had poorer primary patency of the vascular reconstruction, however, and were at increased risk for symptomatic ipsilateral progression of PAD. Multivariate analysis showed that depression was a significant and independent predictor of ipsilateral progression of PAD and failure of the revascularization. Depressive symptoms were associated with major amputation, perhaps related to the small number of events during the follow-up period.

Although no previous reports have examined the impact of depression on outcomes after lower extremity revascularization, multiple studies have found worse outcomes for patients with depression undergoing CABG.\(^3\)\(^{10}\) Similar to the present study, depression was associated with progression of coronary artery disease and recurrent symptoms in a number of reports. Connerney et al\(^8\) observed 309 patients for 1 year after CABG and found that depression was a significant and independent predictor of recurrent cardiovascular events. With 5-year follow-up of 172 patients after CABG, Borowicz et al\(^4\) noted that perioperative depression was associated with recurrent chest pain and repeat coronary revascularization.\(^4\) Another group assessed depression before CABG and prospectively followed 111 patients after surgery. The authors noted that depression was associated with recurrent hospitalization for cardiovascular events at 6 months\(^5\)\(^6\) and with cardiovascular death with 2-year follow-up.\(^5\)\(^6\)

Previous research has examined the biologic plausibility of an association between depression and adverse cardiac events.\(^18\) Biologic mechanisms are present in patients with depression and can increase the risk for cardiovascular events. These include dysregulation of the hypothalamic-pituitary axis and autonomic nervous system, a common genetic vulnerability to depression and coronary heart disease events; increased platelet activation, and increased levels of catecholamine, and serotonin.\(^18\) The association between depression and worse cardiac outcomes may also be mediated by behavioral mechanisms, including noncompliance with diet, medical, or exercise therapy.\(^18\) Further evaluation is needed to understand if these associations also exist for patients with PAD.

Finally, in 2003 the results were published of a randomized trial that examined the association between treatment of depression after myocardial infarction and recurrent myocardial infarction or death. Compared with patients getting “best medical care,” no reduction in event-free survival was found in those receiving depression therapy.\(^19\) Prospective trials are necessary to understand the association between depression therapy, PAD symptoms, and outcomes after PAD intervention.

In the present study, the prevalence of depression among patients undergoing lower extremity revascularization was 36.1%. No previous reports have evaluated the prevalence rate of patients undergoing intervention for symptomatic PAD, and the rate of depression among this patient population was higher than expected.

Results from studies examining the association between depression and PAD in patients with both symptomatic and asymptomatic PAD are conflicting. A recent population-based study of patients aged \( \geq 60 \) found no association between PAD and depression, noting that 8.1% of patients with PAD (ABI <0.90) had depressive symptoms compared with 6.5% of patients without PAD (\( P = \text{NS} \)).\(^20\) Arseven et al\(^21\) however, found that significantly more patients with ABI-diagnosed PAD (24%) had depressive symptoms compared with those without PAD (12%).

Another study from the same group described the association between symptomatic and asymptomatic PAD, depression, and lower extremity functioning.\(^22\) They noted that 21.7% of patients with PAD had a clinically significant number of depressive symptoms. The authors found that the proportion of patients with “leg pain with exertion and rest” rose significantly with increasing number of depressive symptoms. Adjusting for age, race, ABI, number of comorbid conditions, smoking status, and antidepressant drug use, an increasing number of depressive symptoms was also associated with poorer lower extremity functioning.\(^22\)

It should be noted that severely symptomatic PAD, such as in the present study, is characterized by conditions associated with depressive symptoms, such as chronic pain,\(^23\) functional disability, and multiple medical comorbidities.\(^24\) Given the results of the present study and previous research, the high prevalence of depression among patients with symptomatic PAD should be confirmed by prospective trials.

Previous research has examined the prevalence of depression in other patient populations undergoing intervention for an acute medical illness. Depression was present in 27% to 47% of patients before they underwent CABG procedures.\(^25\)\(^26\) Before craniotomy for treatment of a brain
tumor, 36% of neurosurgery patients had significant depressive symptoms.\textsuperscript{27} Overall, approximately 25% of patients diagnosed with cancer have depression.\textsuperscript{28} In the present study, 36% of patients undergoing intervention for symptomatic PAD had been diagnosed with depression, a similar proportion to other patient populations.

The finding in the present study that tobacco use did not predict outcome in the affected limb was unexpected. Previous research has identified an association between tobacco use and poor results after leg revascularization.\textsuperscript{29} In the present study, recent tobacco use or lifetime history of tobacco was not associated with the outcomes of interest. This was most likely due to the high prevalence of tobacco abuse in both depressed and nondepressed patients.

The present study has several limitations. Because of its retrospective design, the results are based on the selected data available in the medical record. However, the VA computerized medical record includes data from all inpatient and outpatient contacts, so that it is unlikely that significant medical events within the VA Hospital system were overlooked.

Patients may have obtained medical care outside the VA Hospital system. We did not review medical records from private-sector hospitals in the region. We believe, however, that it is unlikely that the presence or absence of depression would effect a patient’s decision to seek care from another hospital. Therefore, private-sector care did not likely significantly influence the results of this study.

The conclusions of this report may not be generalizable to women, because the present patient population included only one woman (0.5%). For this retrospective study, data regarding socioeconomic status, activity level and body mass index were unavailable, all of which may have impacted the associations reported in the study.

Finally, patients were diagnosed with depression before the decision was made to intervene for symptomatic PAD. Therefore, some patients in the depression cohort may not have been depressed at the time of intervention but were still receiving antidepressant therapy. Other patients may have developed significant depressive symptoms between the time of depression screening and vascular intervention, yet were not included in the depression group. Although the interval between depression diagnosis and leg revascularization may weaken the associations observed, it should not affect the overall findings of the study.

Prospective data are needed to elaborate on the findings of the present study. Serial assessment of depressive symptoms before and after intervention would result in a more complete understanding of the relationship between depression, depressive symptoms, and symptomatic PAD. As part of a study to assess changes in quality of life after PAD intervention, Johnson et al.\textsuperscript{30} found that patients undergoing surgical bypass (but not angioplasty) had improvement in depressive symptoms.

Concomitant evaluation of chronic pain and functional disability would also be important because these factors are associated with depressive symptoms. In a study of patients with PAD not undergoing intervention, an increasing number of depressive symptoms were associated with worse leg functioning and more leg pain with exertion and at rest.\textsuperscript{22} Understanding the influence of revascularization on these associations would provide important information for the clinician caring for patients with symptomatic PAD.

**CONCLUSION**

Depression is common among patients undergoing intervention for symptomatic PAD. Screening for depression may be of benefit for patients with symptomatic PAD. Depression is associated with worse outcomes after revascularization, with poorer patency and increased risk for recurrent leg symptoms.

**AUTHOR CONTRIBUTIONS**

Conception and design: GC
Analysis and interpretation: GC, JW, HH
Data collection: GC, PZ
Writing the article: GC, JW
Critical revision of the article: GC, JW
Final approval of the article: GC
Statistical analysis: JW

Obtained funding: Not applicable
Overall responsibility: GC

**REFERENCES**


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