Comparison of in-hospital secondary prevention for different vascular diseases

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Abstract
Secondary prevention of coronary artery disease is highly effective and implemented on a large scale. However, studies testing adherence to recommended secondary prevention of other vascular diseases are rare. Our goal was to evaluate whether the kind of vascular disease influences prescription practice of secondary drug prophylaxis at hospital discharge and to which extent secondary prevention is actually complete.

Reference

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Comparison of in-hospital secondary prevention for different vascular diseases

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1. Introduction

The pharmacological secondary prophylaxis of cardiovascular risk factors has proven useful in lowering morbidity and mortality in coronary artery disease, and numerous international recommendations guide physicians towards a more adequate prescription of these drugs [1,2–4]. Over the last few years several studies have demonstrated clear improvements in the pharmacological prevention of coronary artery disease [5–7]. However, the targets are still not met and the most evident gaps may be found in older people, women, outpatients and diabetics [7–16].

As vascular diseases share common risk factors and pathomechanisms, comparable guidelines have been published for peripheral arterial (PAD) and ischemic cerebrovascular (CVD) disease [17–20]. However, studies testing adherence to these recommendations have been performed very rarely for PAD and CVD [21], and this minor attention might hide a reduced adherence to guidelines [11,13,22]. Moreover, previous research only reports prescription rates of the single preventive drugs, and does not analyze overall medication rates and to which degree patients are prescribed a complete set of recommended drugs [5–14,22–23].

The aim of this study was to assess the global prescription rate of secondary prophylactic medications at hospital discharge for each type of vascular disease, to analyze subgroups of patients at particular risk for undertreatment and finally to determine the proportion of patients being prescribed a complete secondary drug prophylaxis.

2. Methods

2.1. Study design and setting

This is a prospective, observational study and its methods were approved by the Cantonal Ethics Committee. The study was performed in the Department of General Internal Medicine at the Ospedale San Giovanni in Bellinzona, Switzerland.

2.2. Study protocol

We consecutively considered and analyzed the hospital discharge information of all patients hospitalized between March 1, 2007 and May 31, 2007 because of acute myocardial infarction (AMI: ST-segment elevation myocardial infarction [STEMI] and non-ST-segment elevation myocardial infarction [NSTEMI]).

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myocardial infarction [NSTEMI]), chronic stable angina (CSA), CVD (transient ischemic attack and ischemic stroke) or PAD. The analysis was done by means of a structured form based on internationally accepted recommendations for secondary prophylaxis of vascular diseases [2–4,18–20]. This study allowed us to observe our steady-state situation of drug prescription, since it was performed without previous information campaign.

From a total of 592 discharged patients, 271 (prevalence of vascular diseases: 46%) were included due to a pertinent diagnosis. We stratified the study population into 6 groups (STEMI, NSTEMI, CSA, embolic and atherosclerotic CVD, PAD) and recorded general patient characteristics and the presence of recommended secondary drug therapy (see point 2.3) in order to compute frequencies. Omission of medications justified by a clear contraindication (e.g. aldosterone antagonist omitted due to severe chronic kidney failure) was disregarded as a deficiency. We then calculated the global prescription rate of secondary prophylaxis (number of prescribed medications divided by the number of indicated medications) and the proportion of patients who were prescribed the complete set of necessary medications (patients lacking one or more required prophylactic drug were defined as incompletely treated). The prescription of certain drugs was dependent on cut-off levels (lipid-lowering therapy, arterial hypertension) or the presence of diabetes mellitus (defined according to WHO-criteria) [2–4,18–20,24]. Neglected measurement of lipid levels during hospital stay accounted as non-adherence as well as co-existent diabetes mellitus and/or arterial hypertension without a corresponding therapy (lifestyle changes and/or pharmacotherapy) or without an explicit suggestion for appropriate follow up.

2.3. Recommended secondary drug therapy and definitions of vascular diseases

For all vascular diseases the following Class I recommendations were required: 1) an antithrombotic agent such as aspirin or clopidogrel (if aspirin contraindicated) or aspirin plus clopidogrel (if current percutaneous coronary intervention with stent implantation), or warfarin (if atrial fibrillation, thrombo-embolic stroke or left ventricular thrombus); 2) a statin, if LDL-C ≥ 2.59 mmol/L (100 mg/dL); 3) an antihypertensive therapy for appropriate blood pressure control (BP < 140/90 mm Hg or BP < 130/85 mm Hg for concurrent chronic kidney disease or diabetes mellitus); and 4) a suitable diabetes management. The prescription of a beta-blocker was mandatory (diltiazem/verapamil if beta-blocker contraindicated) for all patients with AMI and for CSA in case of symptomatic disease. An angiotensin converting enzyme inhibitor or an angiotensin receptor blocker (if ACE contraindicated) was required for STEMI and for CSA with concurrent diabetes mellitus. Decreased left ventricular systolic function (ejection fraction < 40%) was supposed to be treated with an angiotensin converting enzyme inhibitor (or angiotensin receptor blocker) and an aldosterone antagonist.

AMI was defined as the combination of typical symptoms and/or electrocardiographic signs with the characteristic course of biochemical markers of myocardial necrosis (rise of troponin I ≥ 0.1 ng/mL). STEMI was diagnosed in case of ST-elevation in two contiguous leads (≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2–V3 and/or ≥ 0.1 mV in other leads) or a new left bundle branch block. CSA was considered for a patient with known coronary artery disease and stable symptoms and when the current hospitalization was due to other causes. The definition of CVD was based on actual/past clinical evaluation, eventually supported by pathologic findings in brain imaging (in case of ischemic stroke). PAD was defined by typical clinical findings (history and physical examination) and ancillary examinations (invasive and noninvasive testing).

2.4. Data collection

The review process was performed in two steps. The initial step served as an assessment of accuracy between discharge summary reviewers and allowed the estimation of k-values: during the first week of the project two experienced, board registered internists independently examined the same summaries. Reliability across reviewers was consecutively assessed by a third physician and scored using a previous reported scale [25]. Globally, inter-rater agreement was determined excellent (k = 0.86). During the second step of the review process (11 weeks), three internists jointly performed the analysis in order to further improve reliability. Thus, differences between the reviewers’ judgments were resolved by discussion and a consensus was achieved.

2.5. Statistical analysis

All the analyses were done with S-Plus® 7.0 for Windows, Enterprise Developer, Insightful Corp. Differences between groups were tested with chi-square test for contingency tables (exact of Fisher when possible), or two-sided Student’s t test for continuous variables. A multivariate logistic regression was performed to investigate the link between complete treatment adherence for different types of vascular disease and the following factors: gender, age, temporary stay in the Intensive Care Unit (ICU), number of drugs prescribed and length of hospital stay.

3. Results

During this 3-month period 271 consecutive patients were included in the study because of vascular disease diagnosis at discharge: 105 had AMI (28 STEMI and 77 NSTEMI), 86 CSA, 88 PAD and 72 CVD (8 embolic and 64 atherosclerotic). Their main characteristics are shown in Table 1. Women were (mean ± SD) older (76 ± 12 years vs 70 ± 12 years; p < 0.001), had more medications (8.2 ± 4.0 vs 7.3 ± 3.1; p = 0.046) and less AMI (23% vs 48%; p < 0.01) or PAD (24% vs 37%; p = 0.032) than male subjects, but tended to be affected more frequently from CSA (39% vs 27%; p = 0.067). Men suffered more often of multiple vascular disease (33% vs 18%, p = 0.010). Compared to the other groups, patients with PAD had more comorbidities, especially chronic kidney failure (82% vs 39%; p < 0.001), but the 12-month rates of mortality (p = 0.624) and hospital readmissions (p = 0.148) did not differ between groups.

Prescription rates of the single recommended drugs are listed in Table 2 according to the vascular diseases. Globally, an antithrombotic therapy (94%) was better prescribed than a treatment for concurrent diabetes mellitus (47%; p = 0.019), and these rates were independent of the pathology or gender (p = 0.778 for the antithrombotic therapy, p = 0.167 for diabetes mellitus). Patients with STEMI got more frequently a statin (p = 0.002) or an angiotensin converting enzyme inhibitor/angiotensin receptor blocker (p < 0.001) than subjects affected by other vascular diseases. A dual antiplatelet therapy was given to all 21 patients after percutaneous coronary intervention with stent placement. Eleven patients with coronary artery disease presented a contraindication to beta-blockers; in 10 (91%) cases that drug was substituted with either verapamil or diltiazem. After an AMI, the drug was substituted with either verapamil or diltiazem. After an AMI, the drug was substituted with either verapamil or diltiazem. After an AMI, the drug was substituted with either verapamil or diltiazem. After an AMI, the drug was substituted with either verapamil or diltiazem.
Aldactone 25 (0–35.0). There is no evidence that a complete set of medications (Fig. 2) was globally 29.5% (24.1–35.0). The absence of diabetes mellitus resulted in a 3-fold (1.6–35.0) higher chance to be prescribed a full secondary prophylaxis, whereas the other parameters taken into account in the model, namely the sex, age, stay in ICU, duration of stay and number of prescribed drugs, did not have a similar impact. There is no evidence that a complete set of recommended medication was associated with lower 1-year rates of mortality (p = .439) or hospital readmissions (p = .986).

### 4. Discussion

Our study assessing guideline-recommended medical therapy at hospital discharge shows that the global prescription rate varies between the different vascular diseases, though not presenting striking disparities (72.1%–74.5%), that drug prescription significantly depends on age and length of hospital stay, and that the portion of patients receiving complete prescription is considerably low (29.5%).

In coronary artery disease antithrombotic agents, angiotensin converting enzyme inhibitors/angiotensin receptor blockers and statins were prescribed in 96%, 52% and 74%, respectively; findings similar to

### Table 1

Characteristics of patients with vascular diseases.

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>AMI STEMI</th>
<th>NSTEMI</th>
<th>CSA</th>
<th>PAD</th>
<th>CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>5 (18)</td>
<td>23 (30)</td>
<td>53 (62)</td>
<td>72 (82)</td>
<td>1 (12)</td>
</tr>
<tr>
<td>Chronic kidney failure</td>
<td>3 (11)</td>
<td>23 (30)</td>
<td>23 (27)</td>
<td>28 (32)</td>
<td>1 (12)</td>
</tr>
<tr>
<td>Medications ≥40, n</td>
<td>4 (14)</td>
<td>17 (22)</td>
<td>18 (21)</td>
<td>13 (15)</td>
<td>1 (12)</td>
</tr>
<tr>
<td>COPD</td>
<td>2 (7)</td>
<td>9 (12)</td>
<td>14 (16)</td>
<td>18 (20)</td>
<td>1 (12)</td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>0</td>
<td>11 (14)</td>
<td>18 (21)</td>
<td>11 (13)</td>
<td>1 (12)</td>
</tr>
</tbody>
</table>

### Table 2

Prevalence of indicated medication for recommended secondary prophylaxis.

<table>
<thead>
<tr>
<th>AMI</th>
<th>STEMI</th>
<th>NSTEMI</th>
<th>CSA</th>
<th>PAD</th>
<th>CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>93 (82–100)</td>
<td>73 (62–82)</td>
<td>64 (53–74)</td>
<td>52 (42–62)</td>
<td>25 (0–62)</td>
</tr>
<tr>
<td>Clo</td>
<td>79 (64–93)</td>
<td>39 (29–49)</td>
<td>19 (10–27)</td>
<td>29 (20–40)</td>
<td>0</td>
</tr>
<tr>
<td>ASA + Clo</td>
<td>57 (57–89)</td>
<td>35 (25–45)</td>
<td>14 (7–22)</td>
<td>18 (10–26)</td>
<td>0</td>
</tr>
<tr>
<td>Wa</td>
<td>11 (0–25)</td>
<td>29 (18–39)</td>
<td>31 (22–42)</td>
<td>32 (23–42)</td>
<td>87 (62–100)</td>
</tr>
<tr>
<td>AP± Wa</td>
<td>100</td>
<td>95 (90–99)</td>
<td>95 (91–99)</td>
<td>91 (84–97)</td>
<td>100</td>
</tr>
<tr>
<td>BB</td>
<td>71 (54–86)</td>
<td>51 (35–68)</td>
<td>49 (34–64)</td>
<td>nr</td>
<td>nr</td>
</tr>
<tr>
<td>Statins</td>
<td>96 (88–100)</td>
<td>77 (68–87)</td>
<td>59 (49–70)</td>
<td>62 (52–73)</td>
<td>50 (12–88)</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>71 (54–86)</td>
<td>42 (31–53)</td>
<td>50 (46–60)</td>
<td>40 (30–50)</td>
<td>25 (0–62)</td>
</tr>
<tr>
<td>Aldactone</td>
<td>25 (0–75)</td>
<td>50 (20–80)</td>
<td>17 (0–42)</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>DM</td>
<td>42 (17–67)</td>
<td>51 (35–68)</td>
<td>49 (34–64)</td>
<td>45 (27–64)</td>
<td>50 (0–100)</td>
</tr>
<tr>
<td>AHT</td>
<td>93 (81–100)</td>
<td>83 (74–91)</td>
<td>81 (73–90)</td>
<td>78 (69–86)</td>
<td>50 (12–88)</td>
</tr>
</tbody>
</table>

Data in mean±SD [continuous variables] or numbers [%] [categorical variables]; LOS, length of stay; ICU, transitory stay in Intensive Care Unit; AMI, acute myocardial infarction; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; CSA, chronic stable angina; PAD, peripheral arterial disease; CVD, cerebrovascular disease. a Mortality at 12 months. b Total number of readmissions within 12 months (percentage of patients concerned).
those reported in a recent survey of outpatients (97%, 59% and 80%) [7]. Most patients had a lipid profile measured and were successively prescribed a corresponding therapy. On the other hand we do not know whether the prescribed dosages of statins were sufficient to achieve recommended lipid levels. Unexpectedly, concurrent diabetes mellitus was insufficiently treated: for less than half of affected patients an adequate antidiabetic therapy – in whatever form – had been established. Thus, diabetic patients with coronary artery disease seem to be somewhat neglected. This result becomes even more worrisome, when we consider that they were also significantly less prescribed other prophylactic medications. This data confirms the observation that diabetics are less likely to be treated for concurrent dyslipidemia [15].

Global prescription rates of secondary prophylaxis for PAD and CVD are actually similar to those assessed in coronary artery disease. Therefore, vascular diseases with common risk factors seem to receive – at least in our setting – comparable attention. Contrary to other authors, we did not find any significant sex-related differences [11–13]. We were not able to clarify by which mechanism the length of hospital stay affected prescription practices. We speculate that longer hospitalizations were due to more complex clinical courses, the latter probably implicating a temporary suppression of certain prophylactic drugs without reintroducing them at hospital discharge. Once more we noticed an insufficient therapeutic approach towards concurrent diabetes mellitus. At this point it appears mandatory to emphasize, that diabetes was elevated from a major risk factor to a coronary artery disease risk equivalent [26]. The rationale for this change derives from observations indicating a several-fold increased risk of coronary artery disease for diabetic patients, especially for women [27,28]. Although we found similar global prescription rates, the pattern of secondary prevention substantially varied among acute (AMI and CVD) and chronic (CSA and PAD) vascular events according to the then valid guidelines. In this sense we were surprised to note, that especially the lipid-lowering therapy was more actively pursued in STEMI than in CVD. Even though global prescription rates were considered acceptably high, we further investigated the prescription pattern among patients and disease classes. For this purpose, patients lacking in at least one required prophylactic drug were defined as incompletely treated. Surprisingly, adherence to the complete bundle of recommended therapy was homogeneously distributed among vascular diseases but concerned only about 30% of the various studied populations. This finding – important for our institution but not necessarily generalizable to the European cardiovascular community – might all the same lead to a more articulated interpretation of presumably “good prescription practice”: most patients receive good attention but for most of them secondary prophylaxis is still incomplete!

The employ of polypills could theoretically promote more complete cardiovascular prevention, although its feasibility has still to be proven [29]. However, the need for an individually tailored composition might represent an additional difficulty in putting this strategy into practice.

Our study presents some potential limitations. First, this is a pilot project, performed in a unique center and by a limited number of reviewers. Some inherent bias might therefore exist since all investigators were trained together and were working at the same institution. Thus, the generalization of our results has to be confirmed. A second
limitation concerns the method of data collection and the presumption that our results entirely match the established secondary prevention. In fact, our data rely on a meticulous review of the discharge summaries, whereas the effectively instituted secondary prevention depends on the prescription order, directly consigned to the patient. Nonetheless, although these two sources have not been cross-checked, we are sure having credible results, as the patient's prescription order, suitably populated with data from the discharge summary, most probably was not modified later on. Third, the smallness of the analyzed collective implies confirmation of our results, preferably by means of a multicentric study that also involves data from other countries and different races. Finally, “more is not always better!” Even though we meticulously reviewed the discharge summaries we do not know whether the treating physicians had possibly good reasons not to prescribe the whole bundle of prophylactic drugs. In fact, drug interactions, adverse drug events, and prevention of polypharmacy could be very reasonable motivations to do so. Furthermore, we did not evaluate the influenza immunization practice – although strongly recommended as a long-term medical treatment for all patients with coronary artery disease [2–4] – as local general practitioners expect us to let this task to their competence.

In conclusion, our study demonstrates that secondary prophylaxis at hospital discharge for CVD and PAD is comparable to that assessed for coronary artery disease. Nonetheless, the goals are still not met and its considerable underuse observed in elderly patients and the lack of treatment of concurrent diabetes mellitus may result in a worse prognosis [30,31]. Finally, only about one third of the studied collective gets a complete set of recommended prophylactic drugs. Substantial efforts are required to bridge the gap between optimal evidence-based medicine and current practice.

5. Learning points

• There seems to be comparable secondary prevention prescription practice at hospital discharge for the different vascular diseases. However, only few patients get a complete set of recommended prophylactic drugs.

• Elderly and diabetic patients are at high risk for undertreatment.

Acknowledgment

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