Peer reviewed article

Stroke, coronary and peripheral artery disease survey on antithrombotic treatment in Switzerland (START IT)

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Summary

Questions under study: To determine the perception of primary care physicians regarding the risk of subsequent atherothrombotic events in patients with established cardiovascular (CV) disease, and to correlate this perception with documented antithrombotic therapy.

Methods: In a cross-sectional study of the general practice population in Switzerland, 381 primary care physicians screened 127 040 outpatients during 15 consecutive workdays in 2006. Perception of subsequent atherothrombotic events in patients with established CV disease was assessed using a tick box questionnaire allowing choices between low, moderate, high or very high risk. Logistic regression models were used to determine the relationship between risk perception and antithrombotic treatment.

Results: Overall, 13 057 patients (10.4%) were identified as having established CV disease and 48.8% of those were estimated to be at high to very high risk for subsequent atherothrombotic events. Estimated higher risk for subsequent atherothrombotic events was associated with a shift from aspirin monotherapy to clopidogrel, vitamin K antagonist or aspirin plus clopidogrel ($p < 0.001$ for trend). Clopidogrel (12.7% vs 6.8%, $p < 0.001$), vitamin K antagonist (24.5% vs 15.6%, $p < 0.001$) or aspirin plus clopidogrel (10.2% vs 4.2%, $p < 0.001$) were prescribed in patients estimated to be at high to very high risk more often than in those at low to moderate risk.

Conclusions: Perception of primary care physicians regarding risk of subsequent atherothrombotic events varies in patients with CV disease, and as a result antithrombotic therapy is altered in patients with anticipated high to very high risk even though robust evidence and clear guidelines are lacking.

Key words: atherosclerosis; risk; ischaemia; antithrombotic agents

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Introduction

Recurrent atherothrombotic events often occur in patients with established cardiovascular (CV) disease including coronary (CAD), peripheral artery (PAD) and cerebrovascular disease (CVD). Results from the REduction of Atherothrombosis for Continued Health (REACH) registry have shown that one out of six patients with established CV disease suffer from heart attack, stroke, cardiovascular death or hospitalisations for cardiovascular events at one-year follow-up [1]. Patients with ischaemic stroke in Switzerland have a mortality rate of 44% over the following five years and a 20–40% risk of a second stroke [2]. Cerebrovascular disease is the third most common cause of death in Switzerland [3]. Despite contemporary therapy, outpatients with symptomatic atherothrombotic vascular disease experience high rates of recurrent vascular events at 1- and 3-year follow-up [1, 4]. Thus, a change in antithrombotic treatment may be a reasonable measure to improve survival and reduce recurrent ischaemic events and the need for interventional procedures [5]. However, current guidelines of the American Heart Association/American College of Cardiology for patients with coronary and other atherosclerotic vascular disease, peripheral artery disease and patients with stroke [5–8], the American College of Chest Physicians [9–10] and the European

Society of Cardiology [11] recommend the use of a single antiplatelet drug, in particular low-dose aspirin as first choice or clopidogrel in the case of intolerance to aspirin in patients with CV disease. Interestingly enough, although patients with established CV disease vary in risk for subsequent atherothrombotic events, no differentiated recommendation for antithrombotic treatment is given for patients at high risk, e.g. for those with PAD, polyvascular disease or CV disease with multiple risk factors, as robust evidence is lacking.

In this study we sought to identify patients with established CV disease in a large consecutive Swiss outpatient population with the object of evaluating primary care physicians' perception of differences in risk for subsequent atherothrombotic events, and of correlating this risk perception with variations in antithrombotic treatment.

Methods

The STroke, coronary and peripheral ARTery disease survey on antIthrombotic Treatment (START IT) was a large cross-sectional study performed in Switzerland. General practitioners and internists in medical practice across Switzerland were approached and asked to participate in the cross-sectional study. The participating physicians were asked to screen all patients seeking medical advice on 15 consecutive workdays. Data collection consisted of documentation of the number of daily consultations over 15 consecutive working days (weekly documentation form) and of documentation of basic demographic information such as gender, age, atherothrombotic history, cardiovascular risk factors, risk estimation and antithrombotic medication of the patient on a screening sheet called a visit form. The visit form was available in German and French, Italian-speaking physicians being included in either the German or French group.

Medical record documentation was required to establish the presence of CAD, CVD and PAD. Documented CAD consisted of 1 or more of the following criteria: stable angina with documented CAD, a history of percutaneous coronary intervention, a history of coronary artery bypass graft surgery or previous acute coronary syndromes. Documented CVD consisted of a history of transient ischaemic attack, a history of ischaemic or haemorrhagic stroke, a history of carotid stenting or carotid endarterectomy. Documented PAD consisted of 1 or more of the following criteria: symptomatic PAD defined by a history of claudication, asymptomatic PAD defined by an ankle-brachial index below 0.9, a history of percutaneous transluminal balloon angioplasty or stenting, or a history of peripheral bypass surgery. Polyvascular disease was defined as established CV disease in multiple arterial territories (two or more vascular territories with established atherosclerotic involvement).

Risk factors were those documented in the medical records and included diabetes, current smoking, hypercholesterolaemia, arterial hypertension, atrial fibrillation, obesity and a family history of premature CAD. After documentation of the demographic information and risk factors, physicians were asked to estimate the risk of subsequent atherothrombotic events in patients with established CV disease (CAD, CVD, PAD) on the basis of their perception, using a tick box on the visit form allowing a choice between low, moderate, high or very high risk.

Antithrombotic medication was collected from the medical records for all patients. Antithrombotic agents consisted of low-dose aspirin (100 or 300 mg) alone, clopidogrel (75 mg) alone, vitamin K antagonist alone, or a dual antiplatelet therapy using clopidogrel (75 mg) plus ASA (100 mg).

This cross-sectional study was conducted as a field experience report ("Praxiserfahrungsbericht"). The anonymity of the patient's data was strictly maintained and, according to the requirements of the institutional ethical review board, neither approval nor informed consent from the patients was required. This manuscript was prepared in compliance with the STROBE checklist [12].

Statistical analysis

Continuous variables are expressed as mean (SD). Categorical variables are expressed as frequencies and percentages. Comparisons between categorical variables were performed using the Pearson chi-squared statistic. Odds ratios (OR) including 95% confidence intervals (95% CI) unadjusted and adjusted for age, sex, risk factors, and atherothrombotic events defined as ischaemic stroke, transient ischaemic attack, carotid stenting, carotid endarterectomy, stable angina with documented CAD, a history of percutaneous coronary intervention, a history of coronary artery bypass graft surgery, previous acute coronary syndromes, symptomatic PAD, asymptomatic PAD, a history of percutaneous transluminal balloon angioplasty or stenting, or a history of peripheral bypass surgery. Logistic regression analysis with the backwards elimination algorithm, which means that variables are excluded one by one from the model if they do not contribute significantly to the model, were applied to each antithrombotic drug. The dependent variable used in this logistic regression was the prescribed antithrombotic therapy. The samples analysed for the logistic model consisted of 12 282 patients; 157 patients with haemorrhagic stroke and 618 patients with missing data had to be excluded. The risk level low serves as a reference category (odds ratio = 1). A probability of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS™ software version 15.0.

Results

Of 633 primary physicians who were contacted, 381 actively participated in the cross-sectional study. Of those, 245 (64.3%) used the German visit form and 136 (35.7%) the French visit form. Between January and June 2006, primary care physicians screened 127 040 patients seeking medical advice. A mean of 331 patients per medical practice and a mean of 23 patients per day were screened. Patients were consecutively recruited to ensure representative inclusion of the overall pop-

Figure 1

Flow chart of screening, documentation and data analysis of a large Swiss outpatient population.

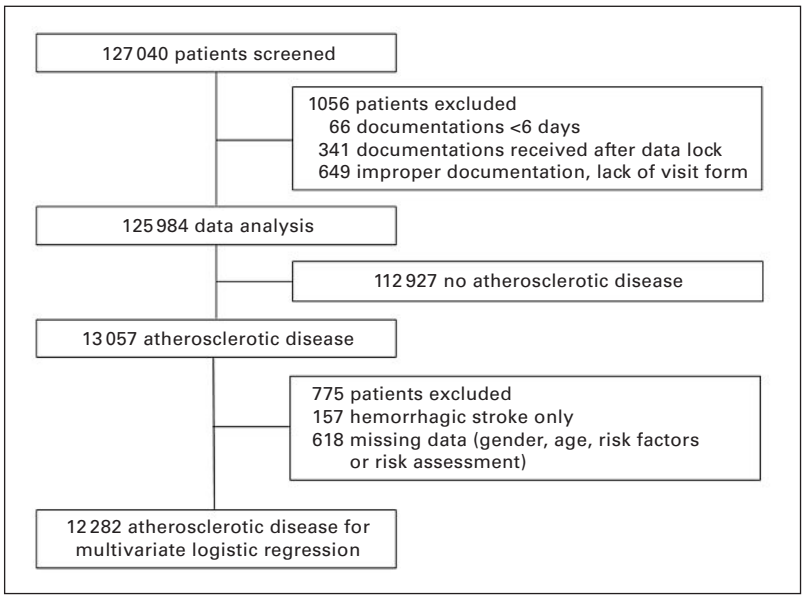


Figure 2

Perception of risk for subsequent atherothrombotic events by vascular territories. CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral artery disease.
§Some patients with CAD, CVD, or PAD are listed in 2 or 3 categories and therefore the total of these 3 categories exceeds 13 057.

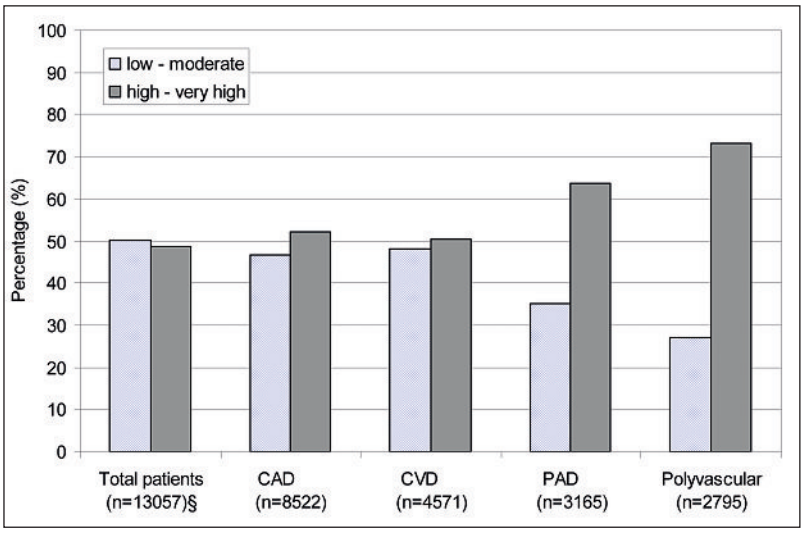
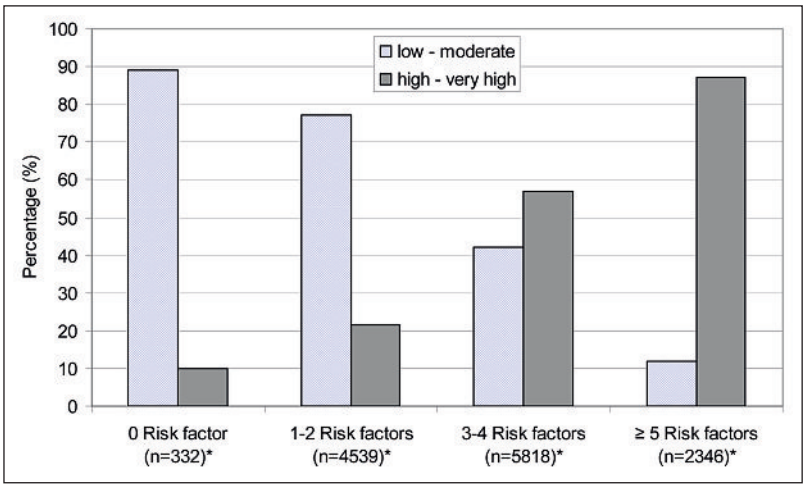


Figure 3

Perception of risk for subsequent atherothrombotic events by increasing cardiovascular risk factors.
* A total of n=22 (0.002%) had missing data and were excluded from this analysis.



ulation. Due to improper documentation and failure to deliver documentation forms within the defined survey period, 1056 (0.8%) patients had to be excluded. Figure 1 shows the detailed flow chart of patients' eligibility, documentation and inclusion in the final analysis. CV disease was identified in 13 057 (10.4%) of 125 984 patients. Of those with CV disease, 65.3% had CAD, 35.0% had CVD, and 24.2% had PAD. Demographic characteristics of the patients with CV disease are given in table 1.

Atrial fibrillation (22.7%) predominated in patients with CVD, hypercholesterolaemia (74.6%) in patients with CAD and smoking (50.3%) in patients with PAD. Overall, 48.8% of all patients were classified as being at high to very high risk for subsequent atherothrombotic events. Low risk was suggested in 11.2% (n = 1461), moderate in 38.9% (n = 5078), high in 35.7% (n = 4657), and very high in 13.1% (n = 1715) of patients. In 1.1% (n = 146) analysis was not possible due to incomplete data.

Perceptions of high to very high risk for subsequent atherothrombotic events are broken down by the vascular territories affected (fig. 2). Patients with PAD and patients with polyvascular disease were perceived to be at high to very high risk for subsequent atherothrombotic events. Patients without or with 1–2 risk factors documented in the medical records were estimated to be at low risk for subsequent atherothrombotic events. However, when a patient's risk factors increased to 3 or more, physicians perceived this as high to very high risk for subsequent atherothrombotic events (fig. 3). The dominant factor for the perception of high to very high risk was the number of risk factors present ($p < 0.001$ for trend). 10% (n = 33) of 332 patients with no risk factors were estimated by the physicians to be at high to very high risk for subsequent atherothrombotic events. This is explained by the fact that the high to very high risk group had more polyvascular disease patients than the low to moderate group (30.3% vs 6.4%).

From a total of 13 057 patients antithrombotic therapy was documented in 51.5% for low-dose aspirin alone, 9.7% for clopidogrel alone, 20% for vitamin K antagonist alone, combination therapy was documented in 7.2% for aspirin plus clopidogrel, 6.8% for other antithrombotic therapy and 4.8% for no antithrombotic therapy.

Of those receiving vitamin K antagonist (n = 2609), 70.2% had single artery disease and 29.8% had polyvascular disease. Overall, 18.1% (n = 2366) of the patients were found to have atrial fibrillation and 65.1% were treated with vitamin K antagonist, 16.6% with aspirin, 3.1% with clopidogrel, 2.8% with clopidogrel plus aspirin and 12.4% with other or no antiplatelet agents.

In an unadjusted analysis the perception of higher risk for future atherothrombotic events was associated with an increase in antithrombotic treatment other than aspirin alone ($P < 0.001$ for trend). The association remained significant after

Table 1

Demographic characteristics and risk factors among patients with atherosclerotic disease.

	Percentage of population*			
	Total (n = 13057)§	CVD (n = 4571)	CAD (n = 8522)	PAD (n = 3165)
Age, mean (SD), y	73.0 (11.4)	75.3 (11.1)	72.8 (11.3)	73.6 (10.9)
Men	57.3	48.3	61.7	59.0
No risk factor	2.5	3.9	1.8	1.0
Diabetes	27.7	25.9	29.1	35.4
Current smoking	37.0	30.5	37.5	50.3
Hypercholesterolaemia	68.5	60.4	74.6	72.8
Arterial hypertension	78.6	79.0	80.7	80.7
Atrial fibrillation	18.1	22.7	19.3	17.9
Obesity	29.0	26.3	31.1	30.7
Family history of premature CAD	35.2	31.8	39.8	36.6
Single vascular disease	78.6	61.7	71.1	43.7
Polyvascular disease	21.4	38.3	28.9	56.3
German	68.8	68.6	70.6	69.8
French	31.2	31.4	29.4	30.2

* Unless otherwise indicated.
§ Some patients with CAD, CVD, or PAD are listed in 2 or 3 categories and hence the total of these 3 categories exceeds 13 057.
CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral artery disease.

Table 2

Unadjusted and adjusted odds ratio of antiplatelet agents and vitamin K antagonist according to increased risk.

	Odds ratio [95% confidence interval]	
Risk estimation	Not adjusted	Adjusted for age, sex, risk factors and atherothrombotic events*
Low-dose aspirin		
Low	1.00	1.00
Moderate	0.89 [0.78–1.01]	1.00 [0.87–1.15]
High	0.48 [0.42–0.54]	0.61 [0.53–0.70]
Very high	0.27 [0.23–0.31]	0.40 [0.33–0.48]
P for trend	<0.001	<0.001
Clopidogrel		
Low	1.00	1.00
Moderate	2.11 [1.56–2.84]	2.30 [1.70–3.13]
High	3.47 [2.58–4.65]	3.94 [2.87–5.40]
Very high	4.09 [2.99–5.59]	4.69 [3.27–6.73]
P for trend	<0.001	<0.001
Vitamin K antagonist		
Low	1.00	1.00
Moderate	1.45 [1.21–1.74]	1.31 [1.06–1.62]
High	2.17 [1.81–2.59]	1.73 [1.38–2.17]
Very high	2.97 [2.45–3.61]	2.03 [1.54–2.66]
P for trend	<0.001	<0.001
Aspirin plus clopidogrel		
Low	1.00	1.00
Moderate	2.14 [1.46–3.13]	1.61 [1.08–2.39]
High	4.29 [2.96–6.21]	2.54 [1.71–3.79]
Very high	6.93 [4.73–10.16]	3.39 [2.21–5.22]
P for trend	<0.001	<0.001

Adjustment was performed for age, sex, risk factors, and atherothrombotic events defined as ischaemic stroke, transient ischaemic attack, carotid stenting, carotid endarterectomy, stable angina with documented CAD, history of percutaneous coronary intervention, history of coronary artery bypass graft surgery, previous acute coronary syndromes, symptomatic PAD, asymptomatic PAD, history of percutaneous transluminal balloon angioplasty or stenting or history of peripheral bypass surgery.

adjustment, showing increasing odds ratios (OR) favouring clopidogrel, aspirin plus clopidogrel or vitamin K antagonist over low-dose aspirin (P <0.001 for trend, table 2).

The frequency of antithrombotic medication in the group with high to very high risk and in those with low to moderate risk is given in table 3. Overall clopidogrel, vitamin K antagonist, aspirin in combination with clopidogrel or other combinations increased significantly in patients estimated to be at high to very high risk for subsequent atherothrombotic events.

Table 3

Rates of antithrombotic and vitamin K antagonist are compared among patients with low to moderate versus high to very high risk.

	Percentage (%) of population		
	Low to moderate risk*	High to very high risk*	P-Value
Monotherapy			
ASA	61.0 (n = 3988)	42.1 (n = 2684)	<0.001
Clopidogrel	6.8 (n = 444)	12.7 (n = 807)	<0.001
Vitamin K antagonist	15.6 (n = 1021)	24.5 (n = 1559)	<0.001
Combination therapy			
ASA plus clopidogrel	4.2 (n = 273)	10.2 (n = 651)	<0.001

* A total of n = 146 (0.01%) had missing data and n = 1484 (11.4%) with other antithrombotic or no therapy were excluded from this analysis.

Discussion

In this large consecutive outpatient survey, CV disease was found in 10.4% of all patients coming to the medical office for any reason. Arterial hypertension and hypercholesterolaemia had a high prevalence, a finding consistent with other registries of stable outpatients with CV disease or multiple risk factors for atherothrombosis [13–14]. In our study patients with polyvascular disease had a prevalence of 21.4%, which is higher than the REACH registry (15.9%) or the CRUSADE registry consisting of non-ST-segment elevation ACS (13%) [13–14]. This finding could be explained by the higher mean age in our study population. Half of the patients were perceived to be at high to very high risk, with highest risk in patients with PAD, polyvascular disease, established CV disease and 3 or more risk factors. The REACH registry [13] reported that patients with PAD are usually regarded as a group at particularly high risk for proximate cardiac ischaemic events, which underscores the validity of the physicians' perception in our study. This may be due to the fact that atherosclerotic disease in PAD often affects multiple vascular territories, resulting in high coincidence with atherothrombosis in other vessel areas [8, 15–16].

Change in antithrombotic treatment other than aspirin alone was correlated with a higher risk perception among physicians. When risk for subsequent atherothrombotic events was perceived to be high or very high, patients were less on aspirin but more on clopidogrel, aspirin plus clopidogrel or vitamin K antagonist, in contrast to current guidelines. The randomised controlled CAPRIE trial [17] previously demonstrated that clopidogrel monotherapy (75 mg) in a head-to-head comparison was slightly superior to aspirin monotherapy (325 mg) in reducing the composite of vascular death, myocardial infarction, stroke and hospitalisation for ischaemic events in a stable secondary prevention population. A post-hoc subgroup analysis for patients with peripheral arterial disease, a relative-risk reduction of 23.8% (95% CI 8.9% to 36.2%) in favour of clopidogrel (p = 0.0028) could be observed [17]. In a post-hoc analysis it was shown that the benefit is further amplified in higher-risk subgroups including patients with a history of ischaemic stroke or myocardial infarction [18], those with diabetes [19] and those with previous cardiac surgery [20]. However, due to high costs, a guideline for clopidogrel prescription is still limited to patients intolerant to aspirin and cerebrovascular insult with additional risk factors [21–23]. The randomised controlled CHARISMA trial [24] showed a non-significant relative risk reduction in the primary efficacy endpoint of dual antiplatelet therapy with aspirin plus clopidogrel over aspirin alone; nevertheless 7.2% of our study population were on dual antiplatelet therapy. Two meta-analyses on randomised controlled trials showed that the addition of clopidogrel to aspirin resulted in a modest reduction in cardiovascular events as compared to aspirin alone, although the hazards of treatment almost match any benefit obtained [25–26]. A subgroup analysis of the CHARISMA trial involving documented prior myocardial infarction, ischaemic stroke or symptomatic PAD demonstrated significant benefit from dual antiplatelet therapy with aspirin plus clopidogrel over aspirin monotherapy [27]. The authors suggested that such patient subgroups may benefit from intensification of the antithrombotic treatment [27], thus potentially explaining the treatment practice of dual antiplatelet therapy in our high risk population.

An interesting point in our study is that vitamin K antagonists are more often prescribed in patients estimated to be at high to very high risk than in those at low to moderate risk independently of the presence of atrial fibrillation. This is particularly interesting in the subgroup of patients with PAD, for whom a published randomised controlled trial [28] showed that a combination of vitamin K antagonists and antiplatelet therapy was not more effective than antiplatelet therapy alone in PAD. It seems that physicians still feel more comfortable providing vitamin K antagonists to patients estimated to be at high to very high risk despite bleeding and discomfort for patients. Anticoagulation is of proven effectiveness in the prevention of arterial thromboembolism in patients with atrial fibrillation [29]. In our study two thirds of the patients with atrial fibrillation were treated with vitamin K antagonists. Nevertheless, anticoagulation treatment is still underused in elderly patients with atrial fibrillation [30], and a more recent study reported that the use of warfarin at discharge was 55% even among those patients considered to be at high risk for stroke [31].

Although it is a large national cross-sectional survey there are certain limitations to this study. The enrolment of patients purported to be consecutive, but in busy practices logistical problems may interfere with consecutive enrolment. Nevertheless, the enrolment at each site was maintained for 15 working days, ensuring absolute consecutive patient enrolment and thus limiting selection bias. Furthermore, classification of the risk of subsequent atherothrombotic events was based on physicians' perception and not on objective findings, making it subject to bias, and no follow-up is provided to predict CV events. Despite some weakness of this survey, it provides insight into a real-world pattern of practice regarding risk estimation and antithrombotic treatment in Switzerland.

In conclusion, our results suggest that patients with CV disease are considered to vary in their risk for subsequent atherothrombotic events, and as a consequence antithrombotic therapy is changed in patients with anticipated high to very high risk even though robust evidence and clear guidelines are lacking.

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