Peer reviewed article

Impact of intracoronary ultrasound guidance on long-term outcome of percutaneous coronary interventions in diabetics – insights from the randomised SIPS trial

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Summary

Background: The Strategy for Intravascular ultrasound (IVUS) guided PTCA and Stenting (SIPS) trial included a prospectively designed subgroup analysis to investigate whether routine IVUS-guidance during percutaneous intervention improves long-term outcome in diabetics.

Methods and results: Consecutive diabetic patients (n = 43) with 57 lesions were randomly assigned to receive provisional stenting with angiographic guidance only (ANGIO) or with IVUS guidance provided by a combined IVUS/variable diameter balloon catheter (IVUS). The combined primary endpoint included death, nonfatal myocardial infarction and target vessel revascularisation (TVR) and was recorded for 28 months. The re-stenosis rate at 6-month follow-up angiography was defined as a secondary endpoint.

A primary endpoint occurred in 6 diabetic patients (31.6%) in the IVUS-group and 11 diabetic patients (45.8%) in the ANGIO-group (relative risk for IVUS, 0.83, 95% confidence interval 0.28–2.35, p = 0.83). Kaplan-Meier analysis suggested that IVUS did slightly attenuate the negative effect of diabetes on long-term event-free survival. The quantitative assessment of follow-up angiography revealed that the incidence of re-stenosis was high in both groups (IVUS: 53% versus ANGIO: 52%, p = 0.94). There was no difference in the mean duration of hospitalisation (11.8 days with IVUS versus 11.2 days with ANGIO, p = 0.83) or total cost ($ 16 725 with IVUS versus $ 16 230 with ANGIO, p = 0.83) during follow-up.

Conclusion: Routine IVUS-guidance during provisional stenting seems to slightly attenuate the negative effect of diabetes on long-term outcome. However, the re-stenosis rate remains very high.

Key words: diabetes; IVUS; angioplasty; stents; outcome

Introduction

Diabetes mellitus is an important risk factor for atherosclerotic cardiovascular disease, which, when present, is associated with increased mortality and morbidity in diabetic patients as compared with non-diabetic patients [1–4]. Diabetics represent ca. 20% of patients referred for percutaneous coronary intervention (PCI) [5, 6]. Unfortunately, diabetics have significantly increased rates of clinical events and re-stenosis after PCI [7–11]. Although the use of stents [12] and abciximab [13] has slightly improved outcome of diabetics following PCI, patients with diabetes treated with current techniques still have lower event-free survival compared with non-diabetics [6].

Intravascular ultrasound (IVUS) is a tomographic imaging technique that has contributed to our understanding in many areas of interventional cardiology with its unique capability to assess the extent of vessel remodelling, plaque morphology, and exact vascular dimensions. IVUS guidance has been shown to improve procedural results [14–17] and reduce the need for subsequent target vessel revascularisation (TVR) [15–17] after PCI. However, the most recent multicentre study failed to show a benefit of IVUS-guidance for primary stenting [18]. The impact of IVUS-guidance on long-term outcome in diabetics is currently unknown. The Strategy for IVUS guided PTCA and

No financial support declared.

Stenting (SIPS) trial [16] included a prospectively designed subgroup analysis to investigate whether routine IVUS-guidance improves long-term outcome in diabetics.

Methods

Patient population

Consecutive diabetic patients undergoing planned intervention (n = 43) with 57 lesions were randomly assigned to receive provisional stenting with angiographic guidance only (ANGIO) or with IVUS guidance provided by a combined IVUS/variable diameter balloon catheter (IVUS). The protocol of this study was approved by the institutional review board, and all patients provided written informed consent.

Procedure

Procedural details have been described in detail elsewhere [16]. In brief, in the IVUS group, cases were performed with a combined IVUS/variable diameter balloon catheter [19] (Oracle Focus™, Jomed, Rancho Cordova, California). A provisional stenting strategy was employed. When the result was unsatisfactory either by angiographic assessment or owing to failure to achieve the pre-defined lesion lumen area of >65% compared to the surrounding reference lumen area, stenting was employed. In the angiographic group, stent use was at the discretion of the operator based only on angiographic analysis. The use of online quantitative coronary angiography (QCA) was recommended by the study protocol in both groups but was ultimately left to the discretion of the operator. Intravenous glycoprotein IIb/IIIa inhibition was not used in these patients.

Follow-up and endpoints

All patients were asked to return for follow-up angiography at 6-months. In addition, patients were contacted at 18 and 28 months and hospital records of our institution reviewed at 28 months for all patients. The medical records of patients suffering adverse events at other hospitals were also obtained and reviewed. Myocardial infarction was defined as typical chest pain at rest followed by an increase in creatine phosphokinase (CK and CK-MB beyond 2×, and 5× the upper limit of normal respectively after coronary artery bypass grafting) or new Q-waves in the electrocardiogram. The combined primary endpoint included death, non-fatal myocardial infarction and target vessel revascularisation (TVR). The re-stenosis rate at 6-month follow-up angiography was defined as a secondary endpoint.

QCA

For QCA, cineangiograms were analysed in a core laboratory unaware of clinical data. Baseline, post-procedural and follow-up (6-month) cineangiograms were analysed with an automated edge-detection algorithm (CAAS II). The reproducibility and accuracy of measurements performed in this laboratory have been reported previously. Specifically, the long term variability for repeated measures (2.3 years) of sequential angiograms was 0.34 mm (stenosis diameter), 0.66 mm (reference diameter), and 6.52% (percentage of stenosis diameter) [20]. The minimal lumen diameter (MLD) of the target lesion, the user defined reference (closest normal appearing segment proximal to the lesion), and the degree of stenosis (percent) were measured in the single worst view on the basis of the baseline angiogram. The acute gain in the diameter of the target lesion was defined as the MLD immediately after the intervention minus the MLD at baseline. Late loss was defined as the MLD immediately after the intervention minus the MLD at six months. The net gain was defined as the MLD at six months minus the MLD at baseline. The loss index was defined as the late loss divided by the acute gain. Re-stenosis was defined as more than 50 percent diameter stenosis at follow-up.

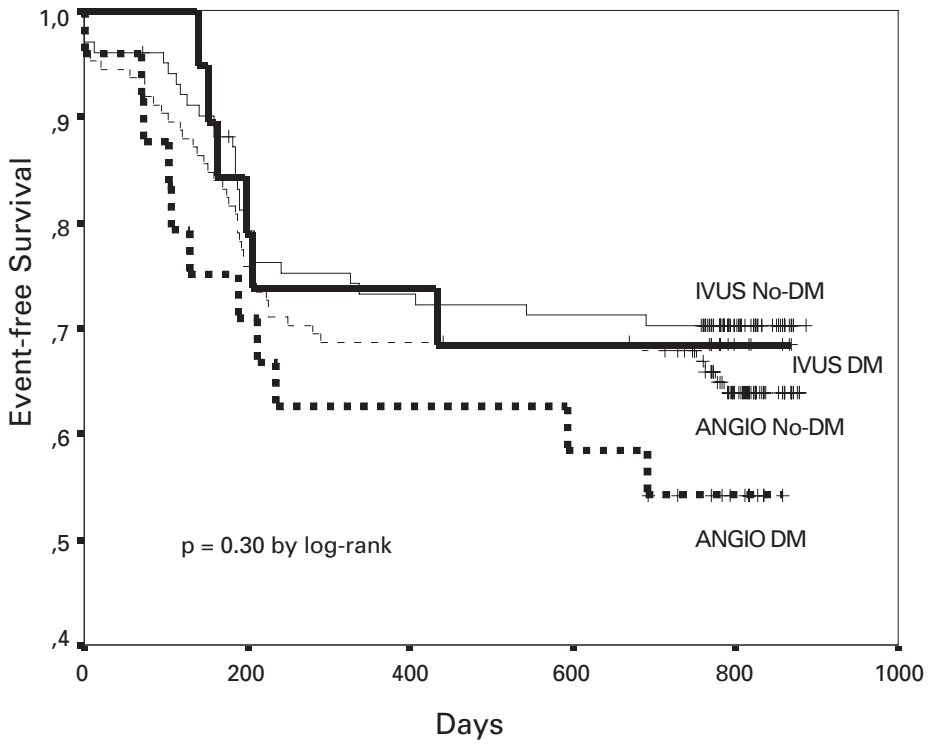

Figure 1

Event-free survival in diabetics with IVUS (IVUS DM), diabetics with ANGIO (ANGIO DM), and non-diabetics with IVUS (IVUS No-DM) or ANGIO (ANGIO No-DM). IVUS seems to attenuate the negative effect of diabetes.

Costs

Direct costs were gathered for the initial hospitalisation and for cardiac related hospitalisations during a two-year follow-up period. These included costs for catheter laboratory resource use, catheter laboratory personnel, inpatient care and TVR. In addition, cost for cardiac medication and indirect costs were calculated. Details of the cost calculation have been described elsewhere [21].

Statistical analysis

Discrete variables were expressed as counts, continuous variables as means ± SD. Comparisons were made among continuous variables using analysis of variance (ANOVA) for independent samples. Comparison of discrete variables was performed using chi-square tests. All hypothesis testing was two-tailed. P-values <0.05 were considered significant. Cox Proportional-Hazards regression analysis was used for the calculation of the relative risk with IVUS for the primary endpoint. The survival curves were generated with the Kaplan-Meier estimator. The statistical analyses were performed using the SPSS/PC (version 10.0, SPSS Inc., USA) software package.

Results

Baseline patient and lesion characteristics were well matched between the groups (table 1). Two-thirds of patients had suffered a previous myocardial infarction, left ventricular function was on average modestly impaired. More than half the lesions were complex (ACC/AHA lesion type B2 or C), one third were re-stenotic. The mean lesion length was 11 mm with IVUS and 10 mm with ANGIO. The balloon-to-artery ratio was 1.05 and 1.06, respectively. Stents were placed in ca. 50% of lesions. QCA-analysis (table 2) revealed that at baseline the reference diameter was slightly larger in the IVUS-group (3.09 mm versus 2.82 mm, p = 0.11). The diameter stenosis was 81% in the IVUS-group and 77% in the ANGIO-group. The acute gain was slightly higher with IVUS (1.85 mm versus 1.60 mm, p = 0.16). However, the MLD of the lesion was only non-significantly higher in the IVUS-group immediately after the intervention (2.44 mm versus 2.26 mm, p = 0.25).

Clinical follow-up was complete in all 43 patients (100%). A primary endpoint occurred in 6 diabetic patients (31.6%) in the IVUS-group and 11 diabetic patients (45.8%) in the ANGIO-group (relative risk for IVUS, 0.83, 95% confidence interval 0.28–2.35, p = 0.83). Kaplan-Meier analysis suggested that IVUS did slightly attenuate the negative effect of diabetes on long-term event-free survival. Two diabetic patients died, one in the IVUS-group and one in the ANGIO-group (table 3).

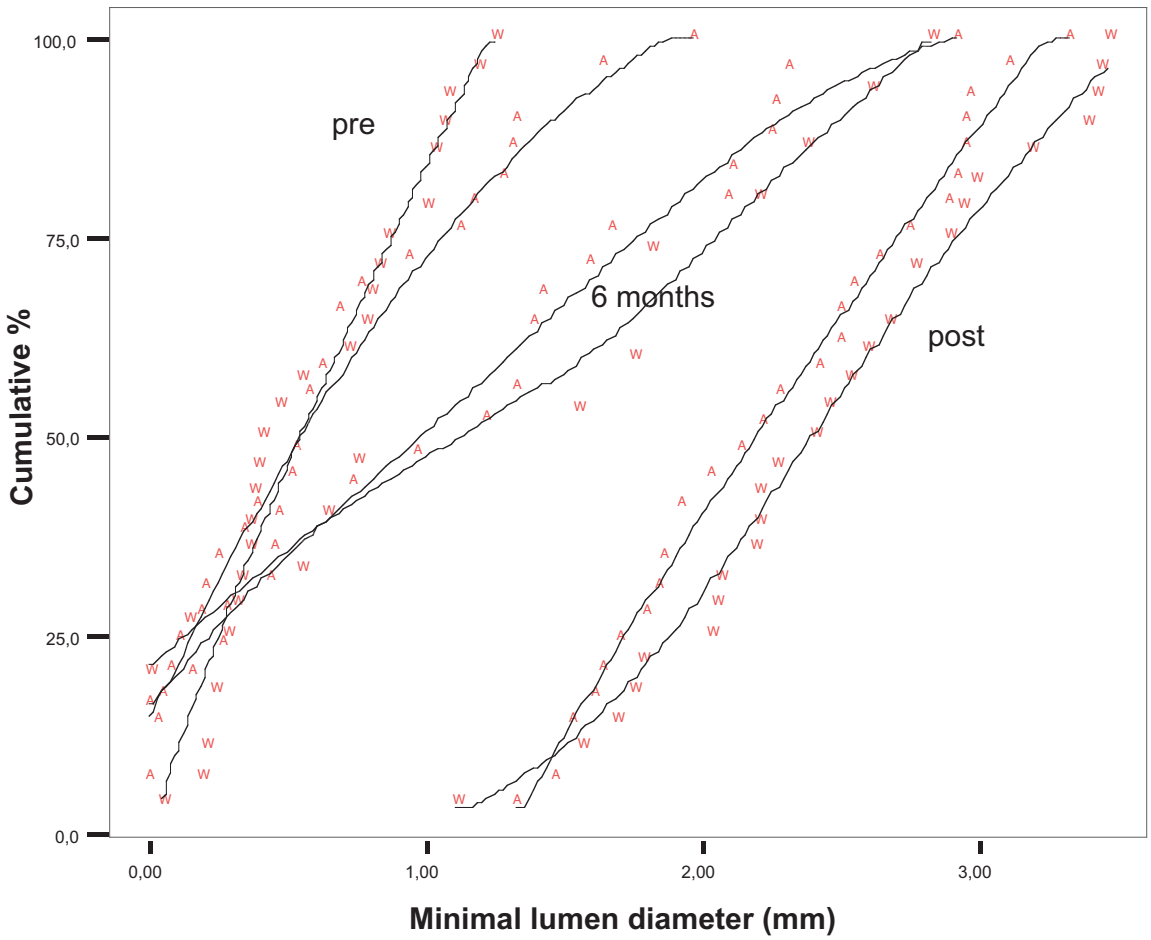

Figure 2

Distribution of lesion minimal lumen diameters at baseline (pre), immediately after the intervention (post), and at 6 months in patients assigned IVUS (bold) or angiographic guidance.

There were no non-fatal myocardial infarctions. TVR was performed in 5 patients (26%) with IVUS as compared to 10 patients (42%) with ANGIO (p = 0.35). There was no difference in the mean duration of hospitalisation (11.8 days with IVUS versus 11.2 days with ANGIO, p = 0.83) or total cost ($ 16 725 with IVUS versus $ 16 230 with ANGIO) during follow-up.

Quantitative assessment of follow-up angiography was possible for 40 lesions (70%). The MLD (1.27 mm versus 1.11 mm), the percent diameter stenosis (61% versus 58%) and the incidence of re-stenosis as the secondary endpoint of this study (53% versus 52%, p = 0.94) were all very similar in both groups. In addition, there was no significant difference in late loss, net gain or loss index.

Discussion

This is the first study that investigates the impact of routine IVUS-guidance for PCI on long-term outcome in diabetic patients. Although IVUS seems to slightly attenuate the negative effect of diabetes, re-stenosis rates remain very high. Consequently, the duration of hospitalisation and total

Table 1

Baseline patient, lesion and procedural characteristics.

	IVUS n (%)	ANGIO n (%)	p-value
Patients (n)	19	24	
Lesions (n)	28	29	
Age (years)	65 ± 8	63 ± 7	0.25
Sex (female)	7 (37)	4 (17)	0.14
Height (cm)	169 ± 8	170 ± 7	0.78
Weight (kg)	83 ± 14	80 ± 11	0.46
Hypercholesterolaemia	16 (84)	24 (88)	0.76
Hypertension	12 (63)	16 (67)	0.82
Smoking	9 (47)	10 (42)	0.92
Prior myocardial Infarction	12 (63)	16 (67)	0.82
Three vessel disease	10 (53)	12 (50)	0.87
Left ventricular function (0–3) (0 = excellent, 3 = severely impaired)	0.8 ± 0.6	0.9 ± 0.8	0.73
ACC/AHA lesion type			
B2	9 (32)	16 (55)	0.08
C	6 (21)	2 (7)	0.12
Re-stenosis	10 (36)	9 (31)	0.71
LAD	8 (29)	11 (38)	0.46
LCX	8 (29)	12 (41)	0.32
RCA	6 (21)	6 (21)	0.95
SVG	0	6 (21)	0.01
Lesion length (mm)*	11.2 ± 8.1	9.7 ± 5.4	0.42
Stent placement	15 (54)	14 (48)	0.70
Balloon diameter (mm)*	3.12 ± 0.61	2.91 ± 0.47	0.18
Maximal inflation pressure (atm)	13.1 ± 3.4	13.4 ± 12.1	0.91
Ballon-to-artery ratio*	1.05 ± 0.20	1.06 ± 0.16	0.78

* by Quantitative Coronary Angiography.
LAD denotes left anterior descending, LCX denotes left circum-flex, RCA denotes right coronary artery, SVG denotes saphenous vein graft.

Table 2

Quantitative coronary angiographic analysis in 57 target lesions before and after intervention.

	IVUS (n = 28)	ANGIO (n = 29)	p-value
Before intervention			
Reference diameter (mm)	3.09 ± 0.60	2.82 ± 0.62	0.11
MLD (mm)	0.60 ± 0.36	0.66 ± 0.57	0.62
Stenosis (%)	81 ± 11	77 ± 18	0.38
Immediately after intervention			
Reference diameter (mm)	3.15 ± 0.56	2.89 ± 0.56	0.09
MLD (mm)	2.44 ± 0.64	2.26 ± 0.58	0.25
Stenosis (%)	22 ± 18	21 ± 18	0.86
At 6 months			
Reference diameter (mm)	3.12 ± 0.63	2.71 ± 0.60	0.05
MLD (mm)	1.27 ± 1.02	1.11 ± 0.89	0.61
Stenosis (%)	61 ± 30	58 ± 32	0.76
Re-stenosis	8 (53)	13 (52)	0.94
Gain or loss			
Acute gain (mm)	1.85 ± 0.67	1.60 ± 0.64	0.16
Late loss (mm)	1.26 ± 1.07	1.10 ± 0.85	0.61
Net gain (mm)	0.71 ± 0.98	0.55 ± 1.03	0.63
Loss index	0.62 ± 0.57	0.84 ± 0.83	0.38

MLD denotes minimal lumen diameter of the stenotic segment. Acute gain, late loss, net gain and loss index are defined in the Methods section.
Data are expressed as mean ± SD

Table 3

Outcomes during 2-year follow-up.

	IVUS n (%)	ANGIO n (%)	p-value
Primary endpoint	6 (32)	11 (46)	0.32
Death	1 (5)	1 (4)	0.87
Non-fatal myocardial infarction	0	0	1.00
Target vessel revascularisation	5 (26)	10 (42)	0.30
Days in hospital	11.8 ± 10.5	11.2 ± 8.8	0.83
Total cost (US$)	16 725 ± 7519	16 230 ± 7371	0.83

costs during the two-year period were very similar in both groups.

One major reason for the limited impact of IVUS may have been the failure to achieve a significantly higher MLD immediately after the intervention in the IVUS group. Although the acute gain was 0.25 mm and the final MLD 0.18 mm larger in the IVUS group, these differences did not reach statistical significance and proved too little to provide a statistically significant long-term benefit. The balloon-artery-ratios were identical in both groups. Therefore, the IVUS information on exact vessel dimensions did not result in a more aggressive balloon sizing. The design of the SIPS study, by recruiting consecutive patients, allows the extrapolation of these findings into clinical practice.

As patency of the target vessel at 6-month follow-up angiography [22] has recently been demonstrated to be a key determinant of survival in diabetic patients after PCI, a significant improvement in interventional techniques seems of utmost importance. Whether the introduction of novel sirolimus-coated stents [23] will solve the "PCI-diabetes-dilemma" or whether the indication for bypass surgery [6, 7] and medical therapy will have to be expanded in diabetics awaits further study.

This study has several limitations. Firstly, compared to angiography, the clinical experience with IVUS criteria is limited. The IVUS strategy used in the SIPS study was based on the best validated criteria for balloon sizing and assessment of PTCA and stent results at the time of study initiation. However, recent findings suggest that using absolute [24] rather than relative cut-off values for final lumen areas might be a more discriminatory use for the IVUS information. Various ongoing studies will help define ideal criteria that may translate into additional clinical benefit for patients receiving IVUS-guided procedures. Secondly, this study is based on a predefined subgroup of the SIPS trial. The numbers are too small and not sufficiently powered to draw final conclusions, but they can be used to generate hypotheses. A large trial in diabetics only would be necessary in order to reach definitive conclusions.

In conclusion, routine IVUS-guidance during provisional stenting seems to slightly attenuate the negative effect of diabetes on clinical long-term outcome. However, the angiographic re-stenosis rate remains very high.

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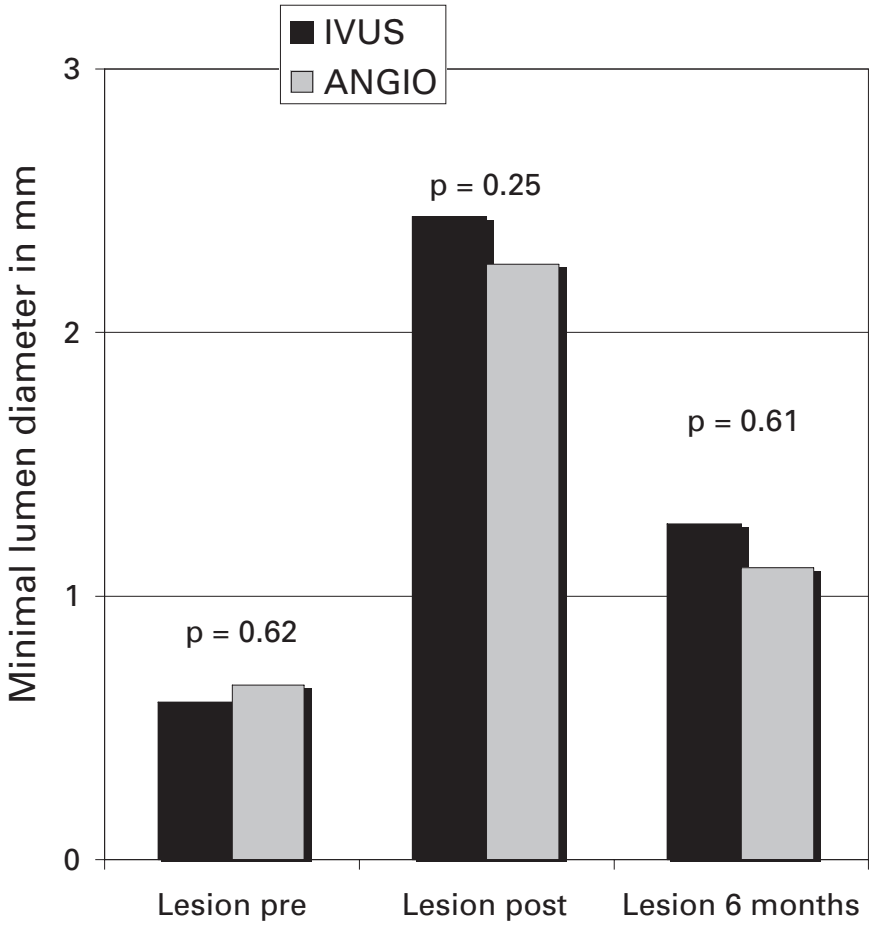

Figure 3

Minimal lumen diameter at the lesion at baseline (pre), immediately after the intervention (post), and at 6 months follow-up in the IVUS and ANGIO group.

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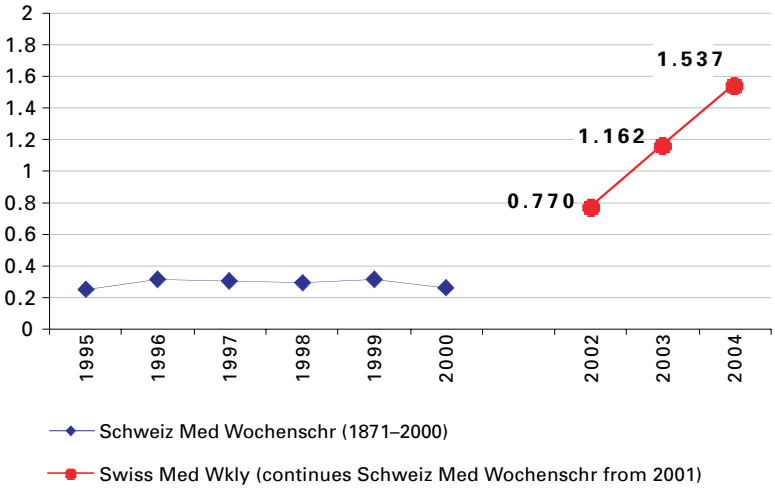

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