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The IST Registry

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■ Das IST-Register

■ **Zusammenfassung** Die intrakoronare Brachytherapie hat sich in Europa und in den USA als evidenzbasierte Behandlungsmethode der In-stent-Restenose etabliert. Ziel des IST-Registers ist es, möglichst vollständig alle in Deutschland intrakoronar bestrahlten Patienten zu erfassen und ihren klinischen Verlauf über fünf Jahre zu beobachten. Um die Mitarbeit zu erleichtern, ist der zu erhebende Datensatz knapp gehalten. Sämtliche Daten werden online eingegeben. Jedes teilnehmende Zentrum kann die wichtigsten Parameter jederzeit im Vergleich zur Gesamtheit aller Zentren über das Internet abrufen. Derzeit wird das Novoste™-System in 58 Katheterlabors und das Guidant™-System in 16 Labors angewendet, einige Zentren benutzen beide Systeme. Da in Deutschland die Anforderungen an den Strahlenschutz für die intrakoronare Anwendung von Gammastrahlen sehr streng sind, wird das Cordis™-Gamma-System in Deutschland lediglich in einem Labor verwendet. In einer ersten Analyse von 332 bestrahlten Stenosen war zu beobachten, dass es selbst nach sechsmonatiger Einnahme von Clopidogrel (zusätzlich zu ASS) zu späten Gefäßverschlüssen kommen kann – ohne dass neue Stents im Rahmen der Brachy-

therapie implantiert wurden. Somit sollte Clopidogrel für mindestens ein Jahr zusätzlich zu ASS eingenommen werden.

Bei derzeit ca. 270 intrakoronar bestrahlten Patienten pro Monat in Deutschland wird das IST-Register wichtige Daten zur Langzeitbeobachtung liefern und eine Grundlage für zukünftige Verhandlungen mit den Kostenträgern sein. Derzeit werden weder die ärztliche Leistung noch die Materialkosten für die intrakoronare Brachytherapie separat bzw. adäquat erstattet. Ferner kann das IST-Register als vergleichende Datenbank für den Langzeitverlauf nach Implantation von antiproliferativ beschichteten Stents herangezogen werden.

■ **Schlüsselwörter** PTCA – PCI – Stent – Brachytherapie

■ **Summary** Intracoronary brachytherapy has been established in Europe and the US as an evidence-based treatment of in-stent restenoses. The objective of the IST Registry is to register all patients treated in Germany with intracoronary radiation and to observe the clinical outcome for a duration of 5 years. The required set of data for each patient is kept to a minimum to encourage participation. All data are entered online. In the internet,

each participating site can, at any time, check their most important parameters and compare them with those of other sites. Presently, the Novoste™ System is used in 58 catheter labs and the Guidant™ System in 16, while several sites use both. The requirements regarding radiation safety in intracoronary application of gamma radiation are very strict in Germany, so the Cordis™-Gamma System is used in only one German lab. In a first analysis of 332 radiated stenoses, it

was observed that late vessel occlusion could occur even after 6-month administration of clopidogrel (in addition to ASA) – without new stents being implanted within the brachytherapy session. Clopidogrel should thus be administered in addition to aspirin for at least a year.

Ca. 270 patients per month receive intracoronary radiation in Germany, so the IST Registry will provide important data regarding long-term observation and a foun-

ation for future negotiations with insurance companies potentially bearing the costs. At present, neither the physician's service nor the material costs are reimbursed. The IST Registry can furthermore be used as a comparative database regarding long-term outcome following implantation of antiproliferative-coated stents.

■ **Key words** PTCA – PCI – stent – brachytherapy

Introduction

Intracoronary brachytherapy has been established in Europe and the US as an evidence-based treatment of in-stent restenoses: it has proven its efficacy in 1,551 patients in eight placebo-controlled, randomized trials with in-stent restenosis as a strict inclusion criteria by significantly reducing the clinical and angiographical restenosis rates (3, 16). As with all new therapeutic strategies bringing short-term success, long-term effectiveness and safety have yet to be determined: initially, intracoronary brachytherapy was limited primarily by the occurrence of later stent thromboses (2, 25, 26). But this problem could be, for the most part alleviated by extended antiaggregation with concurrent administration of ASA and clopidogrel (10, 11, 13). Hereby it must be taken into account that most stent thromboses occur without brachytherapy within the first week, but closer analysis also reveals later occurrence (5, 6, 8). The question whether restenosis occurrence is only delayed after brachytherapy or if a therapeutic benefit can be seen after 3 to 5 years remains to be answered (1, 20, 21, 24).

In Germany, intracoronary brachytherapy is presently performed in 75 cardiac catheter laboratories. The objective of the IST Registry is to enroll all patients treated in Germany with intracoronary radiation and to observe the clinical outcome for a duration of 5 years.

The development of intracoronary brachytherapy in Germany

Since the first intracoronary therapeutic application of radioactive radiation in humans in Europe with a phosphorus-32 Palmaz-Schatz Stent by Hehrlein et al. (4),

intracoronary radiation is nowadays performed via radioactive pellets, wires and "hot" balloons. The first classical afterloading system used in Germany was the Sauerwein/Schneider/Boston-Scientific™ BETAMED System, which was implemented in the European dose-finding study in Geneva, Aalst, Rotterdam and London, and since 1998 also in Essen and Kiel (22). Despite promising results, production of this system was discontinued before it attained CE certification. The first implementation of the Novoste™ System was on November 19, 1998, in Munich before CE certification; the Guidant™ System was first used on July 21, 1999, in Hamburg; and first use of the Cordis™ System was on December 12, 1999, in Bochum. More than 400 patients with different systems have been enrolled within the scope of various clinical trials in Germany (Table 1).

Table 1 Clinical trials regarding intracoronary radiation that are completely or partially (participants in international multicenter trials = *) carried out in Germany

Study	Isotope	Company	City	Patients
BETA-CATH*	Sr/Y-90	Novoste	Munich	55
BRIE*	Sr/Y-90	Novoste	Munich, Dresden, Hamburg	35
ECRIS-I/II	Re-188	–	Ulm	141
Europ. Dose Finding*	Y-90	(Boston-Scientific)	Essen, Kiel	50
GRANITE*	Ir-192	Cordis	Bochum	15
INHIBIT*	P-32	Guidant	Hamburg	9
IRIS*	P-32	Cordis	Heidelberg, Hannover	16
IRT-I/II	Re-188	–	Dresden	> 30
PREVENT*	P-32	Guidant	Berlin, Freiburg	25
RADIANT-Pilot	Re-188	(Radiant)	Munich	11
START*	Sr/Y-90	Novoste	Munich	26

CE-certified afterloading systems

The CE-certified systems approved for routine use in Germany today are the Novoste-BETACATH™ System (beta radiation: strontium/yttrium-90 activity train), the Guidant Galileo™ System (beta radiation: phosphorus-32 wire) as well as the Cordis™ Sytem (gamma radiation: iridium-192, welded pellets). Although the Radiance-RDX™ balloon catheter (phosphorus-32 membrane) received CE certification for lengths of 20 mm and 30 mm, it is not presently commercially available in Europe. Balloon catheters filled with liquid rhenium-188 are at this time not industrially sponsored and therefore also not commercially available.

■ The new Novoste-Beta-Cath™ System

The original version of this system has been presented at length (9, 18, 19); in this version, the application catheter had a diameter of 5 F, making an 8 F guide necessary and radiation of smaller vessels (< 2.7 mm) impossible or

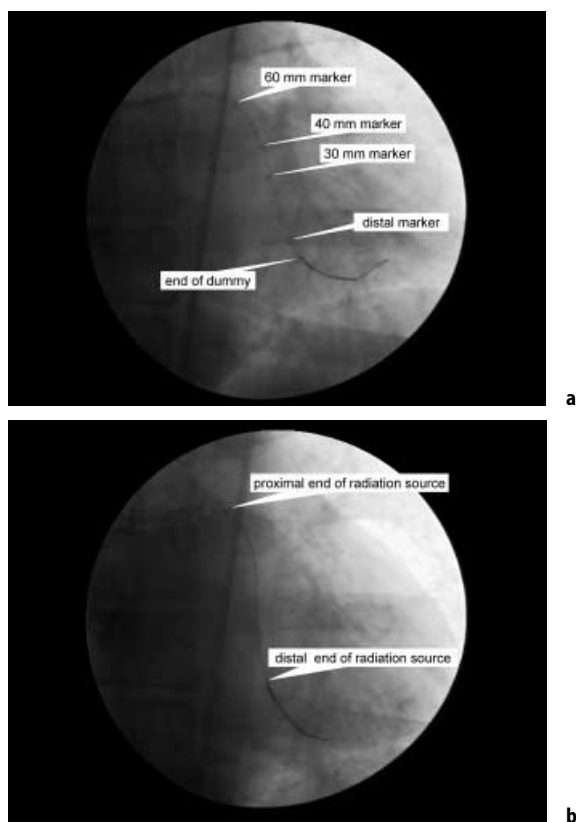


Fig. 1 The new 3.5 F Novoste™ System. **a** The “built-in dummy” shows the markers for the effective radiation length of the 60 mm, 40 mm (and not to be recommended 30 mm) radiation source. The edge effect is already taken into account within these boundaries. **b** after removal of this IST (= Isodose or Injury length Simulation Tool), the active 60 mm-long radiation source is manually delivered.

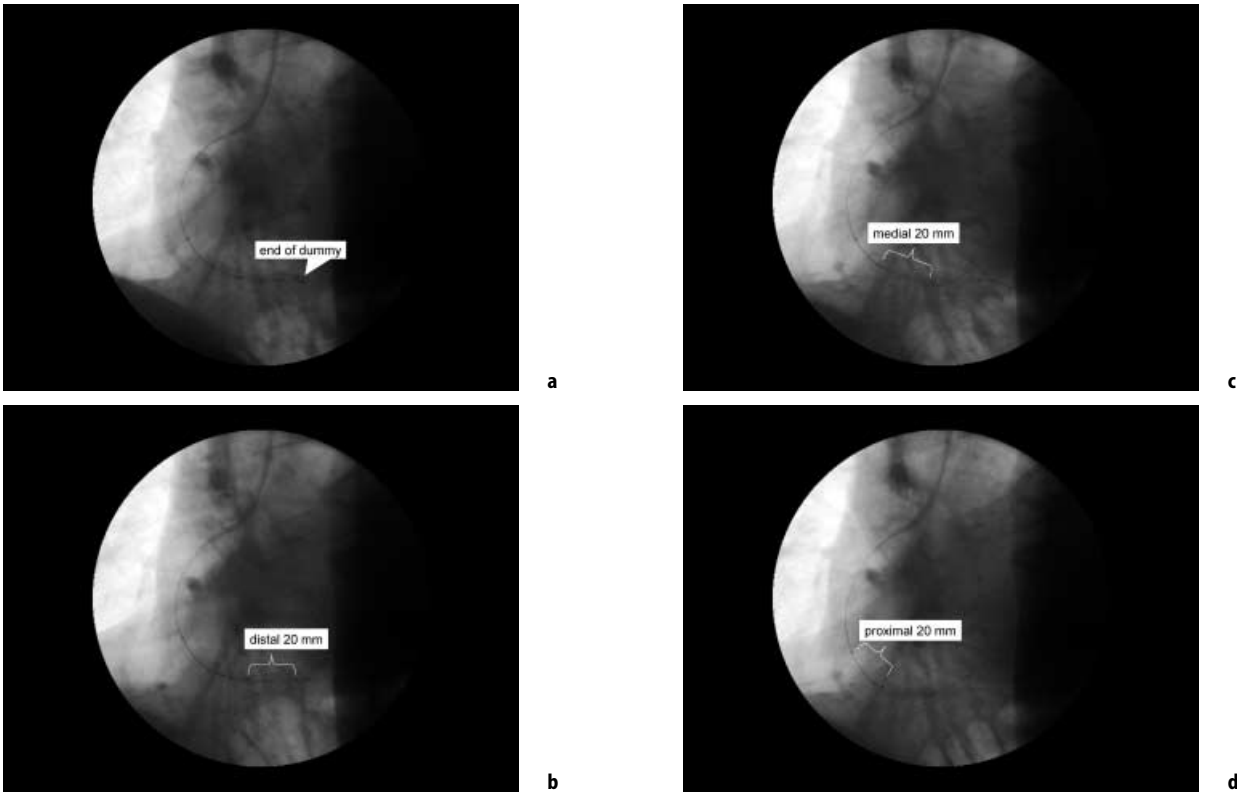
rather leading to occlusion of the vascular lumen. Consequently, the Beta-Cath-Novoste™-3.5 F System has been developed (Fig. 1). The diameter of the activity cylinders was decreased from 0.64 mm to 0.38 mm without altering the activity of 130 MBq (3.5 mCi) nor the length (2.5 mm). But the guide wire was moved to a position external of the application system (a short monorail segment). In this new system, the “dummy run” is performed within the patient without investing more time. The pellets are now held together with a “spring”, so that the activity train is moved in whole and not any more as individual pellets. The nominal activity of the 40 mm radiation source is 2.07 GBq, and for the 60 mm source it is 3.10 GBq. The decrease in pellet size has made brachytherapy possible with a 6 F-guide; and smaller vessels can now be radiated without occluding the lumen.

■ The new Guidant-Galileo™ System

In the new Galileo™ System (Fig. 2) the length of the radioactive source was decreased from 27 mm to 20 mm; radiation of every patient is thus performed in several steps. In contrast to the early system (12), stepping is now performed completely automatically. Special markings allow the activity fall-off at the ends of the radiation catheter to be regarded, so the markings for the 40 mm system are at 32 mm and for the 60 mm system at 52 mm (each with a 4 mm safety margin at both ends). The “dummy run” is still performed as an additional step within the patient. Further progress is demonstrated by the centering balloon (Galileo-3™, in diameters of 2.5 mm and 3.0 mm), which has replaced the earlier spiral balloon.

Table 2 Comparison of both of the new beta-radiation afterloading systems

	Novoste-BetaCath™	Guidant-Galileo™
Radiation source	Strontium/Yttrium-90	Phosphorus-32
Half-life time	30 years	2 weeks
Exchange of sources/ dosimetry	every 6 months	every month
Centering	semi-centered	centered
Source lengths (mm)	40 (30+2x5) 60 (50+2x5)	40 (32+2x4) 60 (52+2x4)
Combined radiation lengths (mm)	40, 60, 80, 100, 120	40, 60, 80, 100, 120
Recommended vessel size (mm)	2.5 – 4.0	2.4 – 3.7
Dosages	18.4 oder 23 Gy at 2 mm from source center	20 Gy in 1 mm vessel depth
Radiation times	4–5 min per total length	30–100 s per segment
Guiding catheter size	6 F	7 F



A comparison of the two new beta radiation after-loading systems is made in Table 2; no trial has been published about either of the two new systems.

Fig. 2 The new Guidant™ System. **a** First, the dummy is motorically inserted and exactly positioned. Then, for the desired 60 mm, the 20 mm-long radiation source is automatically positioned in 3 steps, distal (**b**), medial (**c**) and proximal (**d**).

Fig. 3 Examples of the IST Registry's data entering forms for patient registration, technical details of brachytherapy as well as follow-up.

Patienten

Basisedaten
Stenosedaten
PTCA
IST Vorbereitung
IST Durchführung
Entlassung

Patient

8 TG 16.04.1905
 11 GF 09.04.1951
 128 DD 10.12.1968
 133 AA 12.02.1943
 134 BB 12.02.1950

Sortieren nach:
 ID
 Initialen
 Geb.-Datum

Durchführung der Brachytherapie

Stenosedaten
PTCA
IST Vorbereitung
IST Durchführung
Entlassung
Follow-up

Patienten-ID: 8 Initialen: TG Geb.-Datum: 16.04.1905 Geschlecht: weiblich

Vollständigkeit der Bestrahlung

Bestrahlung nur teilweise durchgeführt

Begründung der unvollständigen Bestrahlung

Fraktionierung

2 Fraktionen

Ereignisse bis zur Entlassung

IST Vorbereitung
IST Durchführung
Entlassung
Follow-up

Patienten-ID: 8 Initialen: TG Geb.-Datum: 16.04.1905 Geschlecht: weiblich

8 Initialen: TG Geb.-Datum: 16.04.1905 Geschlecht: weiblich

Tod: Datum

Myokardinfarkt: Datum

PTCA: Datum 18.02.2001

Bypass-Operation: Datum

andere: Datum

Datum der Entlassung/Verlegung 23.02.2001

Datum des Follow-up 23.02.2001

AKK weit angekommen

AKK abgesetzt mit

Chirurgie Unbekannt

Überlebenszeit abgesetzt mit

Regime erreicht nach ECR 1: Dailische Einstrahlung von der kooperativen Aik-Mit durch AP

wachtbewusstlicher motorischer Ausbruch Ja

Basis des Ausbruchs [] 21

Notwendigkeit von kardialer Intervention Ja

Notwendigkeit von

Verbleiben des kardiellen Gefäßes Ja mit Spätkoronaria

Notwendigkeit von koronarer Intervention Ja mit Spätkoronaria

The IST Registry

The IST Registry (Intrakoronare StrahlenTherapie = intracoronary radiation therapy) is conducted by the IKKF (Institute for Clinical Cardiovascular Research, Munich). Supporting organizations are the German Cardiac Society (DGK), the Association of Hospital-based Cardiologists (ALKK) and the Association of Cardiologists in Private Practice (BNK). The IST Registry is also officially supported by the German Association for Radio-Oncology (DEGRO). The required set of data for each patient is kept to a minimum to encourage participation. All data are entered online (Fig. 3). In the internet, each participating site can, at any time, check their most important parameters and compare them with those of other sites. Presently, the Novoste™ System is used in 58 catheter labs and the Guidant™ System in 16, while several sites use both (Fig. 4). The requirements regarding radiation safety in intracoronary application of gamma rays are very strict in Germany, so the Cordis™-Gamma System is used in only one German lab (Bochum).

■ First results

In the first set of data from Hamburg, Dresden, Bochum and Munich, the frequency of late stent thrombosis occurrence with extended administration of clopidogrel was examined (17). Of the 332 radiated stenoses, 308 were treated with the Novoste™, 9 with the Guidant™ and 15 with the Cordis™ system. Of the stenoses, 77% were in-stent restenoses. The frequency of occurrence of late vessel occlusions with and without myocardial infarction in relation to the implantation of new stents during the same session with brachytherapy can be seen in Table 3.

Table 3 Analysis of late vessel complications in the first patients entered in the IST Registry

	Vessel occlusion	With myocardial infarction	New stents
de novo stenosis			
Novoste (n = 78)	n = 8	n = 6	n = 8
Guidant (n = 0)	–	–	–
Cordis (n = 0)	–	–	–
in-stent restenosis			
Novoste (n = 230)	n = 4	n = 2	n = 1
Guidant (n = 9)	–	–	–
Cordis (n = 15)	n = 1	n = 1	n = 1
Total: (n = 332)	n = 13	n = 9	n = 10

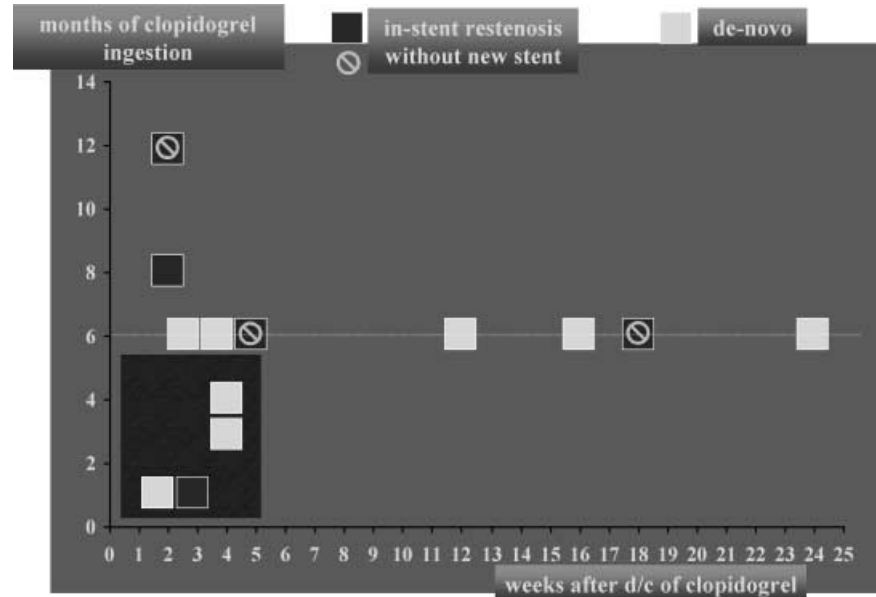


Fig. 4 The geographic distribution of German sites presently using the Novoste™ Systems (N, 58 labs), Guidant™ Systems (G, 16 labs) and the Cordis™ System (C, 1 lab).

Fig. 5 shows the patients with vessel occlusions in relation to the time after discontinuation (x-axis) and the duration (y-axis) of additional clopidogrel administration. It can be seen that late vascular occlusions occur even after taking clopidogrel for more than 6 months – without new stents being implanted for brachytherapy. Because each single, late stent thrombosis should if at all possible be prevented, it can be deduced that – independent of the type of radiated stenosis and independent of the implantation of a new stent during brachytherapy – clopidogrel should be administered in addition to ASA for at least a year. These results of the IST Registry were recently confirmed by the WRIST-12 study (23).

Ca. 270 patients per month receive intracoronary radiation in Germany, so the IST Registry will provide important data regarding long-term observation including the relevance of edge effects (7, 14) and the results in bypass vessels (15) especially for the new afterloading systems. These are important to determine whether the data from clinical trials may be transferred to everyday conditions and provide a foundation for future negotiations with insurance companies potentially bearing the costs. At present, neither the physician's service nor the material costs for intracoronary brachytherapy are reimbursed. The IST Registry can furthermore be used as a comparative database regarding long-term outcome following implantation of antiproliferative-coated stents.

Fig. 5 The occurrence of late vessel occlusions following intracoronary brachytherapy in relation to the time interval between stopping clopidogrel intake and occurrence of a vessel occlusion (x-axis) and the total duration of clopidogrel administration (y-axis).



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