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Contents

Outcome of stenting with BX Sonic and BX Velocity stents (Cordis, Johnson & Johnson) in patients with various forms of CAD

N.V. Kobeshavidze, S.P. Semitko, D.G. Gromov, A.G. Koledinsky, I.S. Topchian, P.Yu. Lopotovsky, D.G. Iosseliani.

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Coronary stenting has become the leading method for the treatment of coronary artery disease. Myocardial reperfusion due to stenting doubtlessly improves the clinical course of the disease, as well as the immediate and the long-term outcome in the majority of cases. At the same time, the long-term in-stent restenosis remains an undesirable adverse event of stenting. The incidence of in-stent restenosis varies depending on each of the stents available. Practical implementation of drug-coated stents substantially decreased the rate of such undesirable complications, however, the problem of in-stent restenosis, though to a smaller extent, still exists, and the cost of drug-coated stents is extremely high and significantly exceeds the cost of bare metal stents. Consequently, the majority of healthcare institution can not refuse from bare metal stents. Thus, the outcome of stenting with various stents has to be thoroughly evaluated in order to define the place for each stent in coronary stenting in every single case.

Thousands of different stents have been implanted in the Moscow City Center of Interventional Cardioangiology. This article is to outline our own experience with BX matrix coronary stents, which were implanted in a single institution and, mostly, by the same specialists and according to a standard protocol, which, in our opinion, increases the homogeneity of the results due to a unified tactics and methods of patient selection, technical aspects of the endovascular procedure and further medical therapy, established in the Center.

According to the protocol, adopted by the Center, all patients after coronary stenting should undergo follow-up examination, including selective coronary angiography, at 6 moths postoperatively. This provides information on both the immediate outcome of stenting and the long-term changes in the patient's condition and coronary arteries.

Purpose of the study was to assess the immediate and the mid-term results of coronary stenting with BX matrix stents of identical design: BX Sonic and BX Velocity (Cordis, Johnson & Johnson, USA). BX stents are fashioned from 316L medical steel using laser processing from a whole steel tubing of certain diameter followed by electronic polishing. The stent element is the so-called "closed type" cell, meaning that the elements form closed or "closed-loop" cells (see Fig. 1). The stents only differ in the delivery system: thus, Raptor balloon catheter is used as a delivery balloon for BX Velocity stent, whereas BX Sonic stent is implanted using U-Pass system. The stents have identical range of lengths and diameters: diameter of 2.25, 2.5, 2.75, 3.0, 3.5 or 4.0 mm (excluding BX Velocity sent with maximum diameter of 5 mm); length of 8 to 33 mm with 5 mm increments. The nominal size is achieved by inflation of the delivery balloon at 10-12 atmospheres (rupture pressure 16 atmospheres). The distal end profile in the stent delivery system is 2.7 Fr.

Clinical data of patients: a total of 2130 stents were implanted in the Moscow City Center of Interventional Cardioangiology between January 2000 and March 2005, including 701 BX stents (176 BX Velocity stents and 525 BX Sonic stents) implanted into 667 native coronary arteries of 561 patients for primary (de novo) atherosclerotic stenosis. Apart of the above mentioned BX stents, 112 stents of another type and manufacturer were implanted into 104 coronary arteries in 81 of the 561 patients (comprising

Fig. 1.

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Table 1. Clinical manifestations, medical history and laboratory findings of patients (n=561).

Parameter	Number
Mean age	58±12.4 years
Men	472 (84.1%)
Basic diagnosis:	
Class 2-4 angina	350 (62.4%)
Unstable angina	138 (24.6%)
MI	73 (13%)
LVEF ≤40%	70 (12.4%)
Diabetes mellitus	68 (12.1%)
History of MI	327 (58.3%)
Hypertension	494 (88.1%)
Excessive body mass	17 (3%)
Smoking	343 (61.1%)
Dyslipoproteinemia	328 (58.5%)
Family history of CAD	201 (35.8%)

14.4%). Clinical manifestations, medical history and laboratory findings in the evaluated patients are summarized in Table 1. Mean age of patients was 58±12.4 years (range 32 to 83 years), the vast majority of patients were men – 472 (84.1%). The cause for examination and treatment was mostly angina pectoris of various NYHA class – 350 cases (62.4%); unstable angina was diagnosed in 138 (24.6%) patients; myocardial infarction – in 73 (13%). In 43 patients with MI the endovascular procedure was performed within the first 6 hours after the onset of MI, the remaining 30 patients had their stents implanted within 14 days after MI.

Diagnostic coronary angiography and endovascular repair were performed according to standard procedure. Angiographic findings were quantified using Hicor software of Coroscop Classic angiography unit (Siemens, Germany) and Axiom Artis FC unit. Results of the selective coronary angiography and endovascular procedures are shown in Table 2.

Table 2. Results of the selective coronary angiography, left ventriculography and endovascular procedures.

Parameter	BX Velocity	BX Sonic	P
2-vessel or multi-vessel disease	47 (32,6%)	133(31,9%)	NS
Location of stenosis:			
LAD	87(49,4%)	279(53,1%)	NS
LCx	20(11,4%)	72 (13,7%)	NS
RCA	50(28,4%)	137(26,1%)	NS
DA or MA	19(10,8%)	37 (7,1%)	NS
Mean referent diameter at the site of endovascular repair (mm)	2,87±0,41	2,98±0,57	NS
Mean stenosis degree (%)	80,2±16,7	78,4±11,3	NS
Minimum lumen diameter at the site of stenosis prior to the procedure (mm)	0,68±0,29	0,7±0,31	NS
Mean lumen diameter at the site of the intervention after repair (mm)	3,06±0,46	3,01±0,32	NS
B2/C baseline stenosis type	115(65,3%)	360(68,6%)	NS
Chronic total occlusion	20 (11,4%)	47 (9%)	NS
Acute occlusion	8 (4,5%)	32 (6,1%)	NS
Mean stenosis length (mm)	14,2±5,7	13,1±6,6	NS
Lumen diameter at the site of intervention after repair (mm)	3,3±0,12	3,01±03,56	NS

Stent deployment was performed at pressure equal or exceeding the nominal value as stated in compliance table and needed to achieve the proper stent diameter and reduce the residual stenosis. The procedure was qualified as successful and non-complicated if: 1) the residual stenosis was ≤20% of the referent diameter of the target segment; 2) TIMI 3 antegrade flow was achieved; 3) there were no signs of threatening dissection, and 4) no occlusion of a significant side branch was present. The absence of recurrent MI, serious rhythm disorders, clinical signs of heart failure, procedural complications at the approach site and other complications (bleeding necessitating blood transfusion or surgical intervention), absence of the need for repeated revascularization was defined as uneventful recovery during in-hospital stay.

Follow-up examination, including selective coronary angiography and ventriculography, was performed at 7.8±2.4 months (mean) postoperatively in 329 patients (58.6%) (patients from other cities usually didn't arrive at the examination, as did the patients with good state of health; certain patients didn't achieve the follow-up time point by the moment of publication). Analysis of the long-term outcome included mortality rate, MI rate, angina recurrence, repeated revascularizations in the target artery. Follow-up study provided information on 389 stents (87 BX Velocity stents vs 302 BX Sonic stents). A stenosis of the artery within the stent (in-stent stenosis) or in adjacent segments (in-segment stenosis) as ≥50% from the reference diameter was judged as restenosis. Occlusion was defined as the absence of antegrade flow (TIMI 0) distal to the stent.

Statistical analysis was performed using Spearman's rank correlation test, Mann-Whitney test (for non-parametric comparison of the mean values) and Wilkokson test (for paired non-parametric comparison of the mean values) to assess statistical significance of the difference between follow-up and baseline values.

Results and discussion: immediate angiographic success was achieved in 692 (98.7%) of 701 stenting attempts. Similar results were obtained by A. Kastrati, who compared outcome of stenting with five different stents (1). An optimal effect in the remaining 9 (1.3%) cases was unattainable due to flow-compromising threatening circular dissection at the distal end of stent in 5 cases; occlusion of a major side branch with ineffective recanalization attempt and subsequent MI in 2 cases; no-reflow effect in another 2 cases (in both cases the intervention was performed in acutely occluded infarct-related coronary artery against the background of AMI). Of the 507 (72.3%) attempts of direct stenting 493 cases (97.2%) were successfully completed. Of the 14 failures to advance stent through

stenosis without predilation, 6 (1.2%) cases were with BX Velocity stents and 8 (1.6%) – with BX Sonic stents. The high per cent of successful direct stenting emphasizes the high patency rate of low-profile stent-delivery system complexes, which coincides with the results of Serruys P. et al (2), who assessed direct stenting. The high patency rate of BX stents were also documented in the article by Wei-Chin Hung et al., who analyzed the results of direct stenting of mammary bypass grafts (3). Interestingly, the low construction profile is accompanied by optimal visualization of stents, allowing for successful positioning of stent during implantation, clear detection of stent during follow-up examination, in addition, stent design and its opacity helps a specialist to assess the lumen and the blood flow within the stent. During stent placement there were no cases of stent dislocation or delivery balloon rupture, which provided predictable outcome of the procedure as regards to its technical aspect. Clinical and angiographic results during hospital stay are summarized in Table 3.

Table 3. Immediate angiographic and clinical results of stenting in studied population.

Parameter	Number
Angiographic success	692 (98.7%)
Direct stenting	507 (72.3%)
Arterial lumen diameter at the site of intervention after the repair (mm)	3.02±0.32
Uneventful recovery	535(95.4%)
Complications:	
Q-wave MI	4(0.7%)/2(0.4%)
Hospital mortality	3(0.5%)
Repeated endovascular procedures	10(1.8%)
Vascular events	8(1.4%)
Acute psychosis	1(0.2%)

There were 3 deaths during hospital stay (0.5%). In one patient with a Q-wave anterior MI causing cardiogenic shock, despite successful LAD reperfusion within the first 6 hours, the death occurred due to progressive left ventricular failure. In two other cases (0.36%) the death was due to acute stent thrombosis within first hours after the procedure causing drug-resistant cardiogenic shock in patients with severe myocardial dysfunction (LVEF≤40%) and a three-vessel disease.

Serious complications at the arterial puncture site (1.4%) included retroperitoneal and subcutaneous hematoma necessitating blood transfusion in one case; pulsatile hematoma in 6 other cases (surgery was required in only one patient, 5 remaining patients were managed by repeated compression at the puncture site). A single case of acute thrombosis of the femoral artery at the puncture site was underwent surgical correction.

Uneventful recovery during hospital stay was observed in 95.4% of cases.

As stated above, follow-up examination was performed in 329 patients, that is, 58.6% of all stented patients included in this study. Angiographic assessment of 389 stents (87 BX Velocity stents vs 302 BX Sonic stents) was performed. Clinical improvement defined as the decrease of NYHA angina class by 1-2 points was found in 266 (80.9%) of the 329 patients studied. Postoperative need for antianginal agents (beta-blockers, nitrates) was observed only in 41.8% of patients, however, there were no significant changes in the dose of ACE inhibitors, calcium channel blockers or diuretics. The rate of "major" cardiac events (death, unstable angina, non-fatal MI) during follow-up was 11.1%. Clinical presentations and history in the long-term period are shown in Table 4.

Table 4. Clinical presentations and history in the control group (n=329).

Table 5 shows the results of follow-up selective coronary angiography.

Table 5. Mid-term findings on follow-up coronary angiography after stenting in general population of patients (n=329).

Parameter	Number of patients
Mortality	2 (0.6%)
Non-fatal MI	13 (4%)
Q-wave MI	9 (2.7%)
Non-Q-wave MI	4 (1.2%)
Unstable angina	21 (6.4%)
Repeated PTCA	117 (35.6%)
Repeated stenting	12 (3.6%)
Coronary bypass grafting	4 (1.2%)

Comparison of the two stents (BX Sonic and BX Velocity) showed no significant changes in values, such as the in-stent restenosis or occlusion. Mid-term follow-up selective coronary angiography in the general population of patients showed the rate of in-stent restenosis and restenosis of the adjacent segments (+5 mm) to be 36.3%, while the rate of in-stent occlusion was 2.5%.

Parameter	BX Velocity	BX Sonic	P
In-segment restenosis	32 (36.8%)	108 (35.8%)	NS
In-stent restenosis	29 (33.3%)	96 (31.8%)	NS
Diffuse restenosis	18 (20.7%)	56 (18.5%)	NS
Local restenosis	11 (12.6%)	40 (13.2%)	NS
In-stent occlusion	2 (2.3%)	8 (2.6%)	NS

We performed correlation analysis (using Spearman's rank correlation test) to detect baseline clinical, history and angiographic factors affecting the clinical course in general, as well as the stent and vessel condition in particular. We found significant correlation between the unfavorable long-term outcome of stenting (restenosis or occlusion) and the vessel lumen diameter ($R=-0.302$; $p<0.03$); stenting site (namely the LAD origin and proximal segment ($R=0.280$; $p<0.04$); morphologically complicated

lesion at baseline (type C) (R=0.270; p<0.04). There was also a trend towards significant correlation between the restenosis and the length of stent (over 13 mm) (R=0.245; p<0.072).

According to the results of the correlation analysis we divided patients between two groups. The first group («high risk» group) included patients with stents (n=133) implanted into the origin or proximal segment of LAD and patients with type C lesion or vessel lumen diameter below 3.0 mm. The second group was comprised of patients with stents (n=55) implanted into RCA, LCx, or LAD middle segment, as well as patients with type A-B1 lesion and vessel lumen diameter over 3.0 mm. There were no significant differences between the groups in other clinical and history parameters. The examination revealed, that the rate of unfavorable mid-term angiographic outcome (restenosis or occlusion) in the first group («high risk» group) was 51.4% vs 8.6% in the second group (p<0,002)!

Conclusion: BX Velocity and BX Sonic matrix stents (Cordis, USA) ensure optimal immediate angiographic outcome in the vast majority of patients (98.7%). Today, when the drug-coated stents, providing lower restenosis rate as compared to usual matrix stents, are used extensively, the role of the latter in management of coronary artery disease becomes particularly questionable: the question is whether one should completely refuse the non-coated stents or they can be successfully used in particular situations under strictly selected indications. The study showed, that the non-coated BX stents can be recommended for type A-B1 lesions in RCA, LCx and LAD middle segment with vessel lumen diameter above 3.0 mm, good immediate effect and mid-term outcome (in-stent stenosis rate of 8.6%), whereas, when used for proximal LAD stenosis (type C), these stents give poor long-term outcome (in-stent stenosis rate of 51.4%), indicating, that other stents, possibly drug-coated, are required in such situations. A number of cooperative studies showed, that the long-term rate of in-stent restenosis after implantation of drug-coated stents is around 6-9%. Correspondingly, the results in the second group of patients are comparable with those of drug-coated stents. This suggests that, in certain cases, bare metal stents can be used instead of expensive drug-coated stents.

References:

1. Kastrati A., Dirschinger J., Boekstegers P. et al. Influence of stent design on 1 year outcome after coronary stent placement: A randomized comparison of five stent types in 1147 unselected patients. Catheter. and Cardiovasc. Intervention, 2000, 50(3), 290-297.

2. Serruys P.W., IJsselmuiden S S., Hout B. Direct stenting with the Bx VELOCITY balloon-expandable stent mounted on the Raptor rapid exchange delivery system versus predilatation in a European randomized Trial: the VELVET trial. Int. J. Cardiovasc. Intervent. 2003, 5(1),17-26.

3. Wei-Chin Hung, Bih-Fang Guo, Chiung-Je Wu et al. Direct stenting of transradial left internal mammary artery graft. Chag. Gung. Med.J., 2003, 26, 925-929.

Drug-eluting stents. New prospects

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Abbreviations:

mRNA — messenger ribonucleic acid,
MAPK — mitogen-activated protein kinase,
ISR — in-stent restenosis,
PDGF — platelet-derived growth factor,
MPA — mycophenolic acid,
CD — Cluster Designation

Commercial success of the companies which have developed and introduced drug-eluting stents (Sirolimus- and Paclitaxel-eluting stents) stimulated similar research performed by other companies. Some of these studies investigated the synthesis of rapamycin derivatives: everolimus and ABT-575 (1, 2, 3, 4, 5, 6, 7). Everolimus (40-O-(2-hydroxyethyl)-rapamycin), which belongs to the macrolides, has complex molecular structure: $C_{53}H_{83}NO_{14}$ (6). As with rapamycin, the receptor everolimus is the intracellular protein FKBP12 (6). Like sirolimus, oral everolimus causes immune suppression (7), and inhibits vascular smooth muscle cells proliferation and neointimal formation in rabbits with stented arteries (3). These data provided basis for the first blinded randomized study of everolimus-eluting stents (4). The study included 42 patients (27 patients with coated stents and 15 with ordinary stents) (4). No significant difference was found in incidence of restenosis and unfavorable outcomes between the two groups during the 1-year follow up. This was probably due to the insufficient sample size (n = 42) (4). Yet, ultrasound examination performed 6 months after stent implantation showed that everolimus significantly ($p<0.001$) delayed neointimal formation (4). The authors made conclusions regarding the safety and antistenotic effect of everolimus-eluting stents (4). These findings were confirmed in more recent studies by the same authors (2). Multicenter randomized placebo-controlled trials are being planned for final determination of the clinical efficiency of the above mentioned stents (2).

ABT-575 (40-epi-(N1-tetrazolyl)-rapamycin) is a semi-synthetic rapamycin derivative with a more complex molecular structure as compared with the parent compound ($C_{52}H_{79}N_5O_{12}$) (5, 8). It has been determined that the receptor for the ABT-575 is the intracellular protein FKBP12 (8). ABT-575 inhibits proliferation of isolated smooth muscle cells (8). ABT-575-eluting stents suppress neointimal formation in porcine coronary arteries (1). The results of the first clinical trial evaluating ABT-575-eluting stents have been published (9). This study included 100 patients (9). After a four month follow-up the authors made a conclusion regarding the safety of these stents (9). Results of multicenter study ENDEAVOR II, which included 1200 patients, and ENDEAVOR III study, which involved a comparative analysis of Cypher stents and ABT-575-eluting stents have not been published yet (9).

Numerous research and clinical centers are currently developing the stents that elute (from Latin elure = to elute, to wash out (10)) compounds that are principally different from rapamycin and Taxol. The high interest for the development of new stents is primarily due to commercial reasons, because stenting is an increasingly popular procedure in clinical practice, and the stent market grows every year. According to P.A. Lemos et al. (11), approximately one million patients in the USA undergo coronary angioplasty annually. Drug-eluting stents are implanted in about 80% of these procedures, approximately 1.5 stent per patient. Besides, sirolimus- and paclitaxel- eluting stents do not provide universal solution to the problem of in-stent restenosis (ISR). Thus, new and more efficient stents than those currently used are likely to be developed. Evidence from several relevant studies is presented below.

In 2002, the first pre-clinical study of angiopeptin-eluting stents was completed in Great Britain (12). Angiopeptin is a protein that selectively inhibits proliferation of smooth muscle cells of blood vessels (12). The study showed this protein to suppress neointimal hyperplasia after implantation of angiopeptin-eluting stents in porcine coronary arteries (12). Hong-Kong clinical trial of angiopeptin-eluting stents involving 14 patients has demonstrated that the stents appear to be safe, delay neointimal hyperplasia and thus may be used for coronary angioplasty in human (13). No multicenter randomized studies of these stents have been performed yet, so their clinical efficiency remains unclear.

It is known that metalloproteinases (enzymes similar to collagenases) play an important role in neointimal hyperplasia (14). Metalloproteinases split collagen used for building the elastic membrane of arteries, thus facilitating the migration of smooth muscle cells into the stent-injured intima (14). Daily administration of metalloproteinase inhibitor GM6001 over 10 months

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has been shown to inhibit neointimal formation in the site of stent implantation in rabbits (15). Besides, studies with smooth muscle cells isolated from rat aorta showed that metalloproteinase inhibitor batimastat is capable of suppressing proliferation of these cells through inhibition of mitogen-activated protein kinase (MAPK) (16). These preclinical data provided the basis for a clinical trial of batimastat-eluting stents in Brazil (17). Regretfully, these stents proved absolutely ineffective in actual clinical setting.

It is well known that female hormones play an important role in regulation of the female reproductive function. However, it was only recently that one of these hormones, specifically estradiol, was shown to regulate migration and proliferation of endothelial cells and smooth muscle cells of blood vessels (18). The experiments were performed with the endothelial and smooth muscle cells isolated from porcine aorta (18). Proliferation and migration of smooth muscle cells were stimulated by adding platelet-derived growth factor (PDGF) to the incubation medium. The study showed that 17β-estradiol completely eliminated stimulating effect exerted by PDGF on the smooth muscle cells (18). However, 17β-estradiol exerts the opposite effect on endothelial cells, enhancing their division and motility (18). Since mitotic activity of cells is known to directly depend on MAPK activity (19), P. Geraldes et al. (18) attempted to determine how female hormones influence the MAPK activity. The authors have determined that 17β-estradiol inhibits MAPK in smooth muscle cells and increases the activity of these enzymes in endothelial cells (18). Therefore, changes of MAPK activity underlie both the mitogenic and antiproliferative effects of 17β-estradiol. Thus, experimental studies suggest that 17β-estradiol may prove an ideal drug for prevention of in-stent thrombosis and restenosis due to enhancement of division and motility of endothelial cells on one hand, and suppression of proliferation and migration of smooth muscle cells on the other hand. Therefore, this hormone should promote neointimization inside the stent while suppressing neointimal hyperplasia. Subsequent pre-clinical and clinical studies have partly supported this suggestion. In the study involving 6 pigs, 17β-estradiol- eluting stents were demonstrated to be associated with 40% slower neointimal growth comparing to uncoated stents (20). In 2004, 17β-estradiol-eluting stents were implanted to thirty patients in Brazil (21). ISRs were detected in 6 months after stenting in two out of 30 volunteers, one of them required repeated revascularization (21). The authors made a conclusion regarding the safety of 17β-estradiol-eluting stents and recommended to perform a multicenter randomized study for complete evaluation of clinical efficiency of the stents (21).

The peptide antibiotic Actinomycin D (Dactinomycin) obtained from the fungus Streptomyces parvullus is approved for clinical use as cytostatic agent in many countries including Russia (22). Additionally, Actinomycin D is widely used in experimental studies as the pharmacological agent capable of selective inhibition of mRNA synthesis on a DNA matrix (19). Considering its high antiproliferative activity, a multicenter blind randomized clinical trial of Actinomycin D-eluting stents has been performed (23). The trial was started without prior non-clinical approbation of Actinomycin-eluting stents. This study included 360 patients (23). Incidence of restenosis was assessed by angiography and by ultrasound examination at 6 month after the stenting procedure (23). The incidence of restenosis after placement of uncoated stents appeared to be 11%, while the incidence of ISR following application of the Actinomycin-eluting stents was 25% ($p<0.03$) (23). Incidence of angina recurrence in the ordinary stent group was 16% versus 37% in the coated stent group ($p<0.001$) (23). Thus, Actinomycin enhances ISR development instead of preventing this process. The cause of this paradoxical effect is unclear. However, two important conclusions may be drawn from this study. Firstly, there are antiproliferative drugs which do not prevent restenosis. Secondly, each new drug-eluting stent should undergo pre-clinical studies. Otherwise health of subjects is placed at risk as it happened in the described multicenter trial (23).

Apart from MAPK, mitotic activity of cells is known to directly depend on protooncogene expression and nuclear oncoprotein synthesis (19). Such genes include c-myc, which is responsible for homonymous protein c-myc (19). Currently, over 10 protooncogenes and nuclear oncoproteins are known (19), but there are no pharmacological agents capable of selective inhibition of any specific gene expression. Selective blockage of gene expression is achieved by antisenses, synthetic oligodeoxynucleotides that are complementary to a specific mRNA, bind it selectively and block its translation in the ribosomes (24). The American group attempted to determine the effects of local blockage of c-myc gene expression on neointimal formation in the stented porcine coronary arteries (25). Immediately after the stenting infusion of antisense to c-myc gene mRNA into the coronary artery was started via “infiltrator delivery system” perfusion device (25). The infusion was performed over 28 days with subsequent immune blotting and morphological evaluation of the stented region (25). It was demonstrated that the antisense completely inhibited the synthesis of c-myc protein and significantly suppressed neointimal hyperplasia (25). Nearly simultaneously with the nonclinical evidence, the results of clinical trial of c-myc gene mRNA antisense termed LR3280 and consisting of 15 deoxynucleotides (5’-AACGTTGAGGGGCAT-3’, letters denote nucleotides) were published (26). Antisense LR3280 was administered in a bolus over 1 minute via intracoronary catheter during the stenting procedure (26). Ultrasound evaluation of coronary arteries 6 months after the intervention showed no significant difference between patients in LR3280 and placebo groups (26). Thus, unlike non-clinical studies, the first clinical trial

of c-myc gene mRNA antisense failed. A possible reason of this failure may be that the oligodeoxynucleotide was administered in a bolus in the clinical trial and for 28 days in the animal study. It is possible that antisense-eluting stents at least as effective as sirolimus-eluting stents may be developed in the near future.

The antibiotic Penicillin is firmly associated by most people with the Penicillium fungi. However, apart from Penicillin, Penicillium genus fungi produce a series of other bioactive compounds, such as the antibiotic Mycophenolate (27). Mycophenolic acid (MPA) is the active metabolite of this antibiotic (27). A comparative study of MPA-eluting stents versus ordinary stents showed 40% decrease of neointimal hyperplasia in pigs caused by the action of this acid (27). These data provided basis for clinical trial of MPA-eluting stents (28). The trial included 55 patients with MPA-eluting stents and 50 patients with uncoated stents (28). Ultrasound and angiographic evaluation 6 months after the stenting procedure showed practically the same neointimal hyperplasia and incidence of restenosis in both groups (28). Subsequent 1 year follow-up with these patients showed no significant difference in the incidence of unfavorable outcomes between the two groups (28). Based on these data A. Abizaid et al. (28) have concluded that the investigated MPA-stents provide no clinical benefit. Still, a possibility exists that MPA-stents with a different amount of Mycophenolic acid may delay the restenosis.

It is known that neointimization of stented human arteries is completed 3–4 months after the stenting procedure (29). Not only does such slow regeneration of the damaged endothelium pose a threat of thrombosis, but it also promotes neointimal hyperplasia. As several researchers suggest (30, 31), heparin and nitrogen oxide produced by endothelial cells suppress proliferation and migration of smooth muscle cells. It has been determined that the endothelial cells that survived the stenting procedure enhance the regeneration of the damaged artery (30). Circulating endothelial cell progenitors play an important role in regeneration of damaged arteries (32, 33). Systemic administration of these cells ensured both fast re-endothelization of damaged areas and suppression of neointimal formation in mice with damaged arteries (34). It has been determined that endothelial cell progenitors adhere to the damaged areas of blood vessels where they differentiate into endothelial cells which suppress proliferation of the smooth muscle cells (34). These data were confirmed by D. Kong et al. in experiments involving balloon dilation of the common carotid artery in rabbits (31). It was quite logical to assume that by enhancing of adhesion of the endotheliocyte progenitor cells in stent-injured arteries, neointimal hyperplasia and ISR may be prevented (30). Bearing this in mind, the research group headed by professor P. W. Serruys initiated a clinical trial of stents with CD34 (CD = Cluster Designation) antibodies (35). This protein is a cellular marker for circulating endothelial cell progenitors (32). The authors of the project presumed that the progenitor cells might bind to the stent surface and ensure fast endothelization of the stent and the stented artery (35). The study included 16 patients. Stents coated with anti CD34 antibodies were implanted in these patients (35). Based upon the results of the study the authors concluded that the stents are safe for patients, are capable to delay neointimal hyperplasia and that a multicenter randomized trials are necessary to determine their clinical efficiency.

A recent study by D.H. Walter et al. (36) has demonstrated that apart from inhibition of cholesterol synthesis, statins also increase the blood count of endothelial cell progenitors. Based on these data cerivastatin-eluting stents were developed (37). However, experimental study involving implantation of cerivastatin-eluting stents and uncoated stents into carotid arteries of rats showed that cerivastatin did not affect re-endothelization of stents (37). At the same time, cerivastatin was demonstrated to inhibit smooth muscle cell proliferation (37). This fact urged the authors to propose a clinical trial of cerivastatin-eluting stents (37). It is quite possible that stents eluting this statin may soon be introduced into clinical practice.

Thus, pre-clinical and clinical studies are currently being performed evaluating everolimus, ABT-578-eluting and a number of other stents (2, 4, 9, 35) that may replace sirolimus- and paclitaxel-eluting stents in the future.

REFERENCES

1. Collingwood R., Gibson L., Sedlik S et al. Stent-based delivery of ABT-578 via a phosphorylcholine surface coating reduces neointimal formation in the porcine coronary model. Catheter. Cardiovasc. Interv., 2005, 65(2), 227-232.

2. Costa R.A., Lansky A.J., Mintz G.S. et al. Angiographic results of the first human experience with everolimus-eluting stents for the treatment of coronary lesions (the FUTURE I trial). Am. J. Cardiol., 2005, 95(1), 113-116.

3. Farb A., John M., Acampado E. et al. Oral everolimus inhibits in-stent neointimal growth. Circulation, 2002, 106, 2379-2384.

4. Grube E., Sonoda S., Ikeno F. et al. Six- and twelve-month results from first human experience using everolimus-eluting stents with bioabsorbable polymer. Circulation, 2004, 109(18), 2168-7211.

5. Pagano T.G. Complete assignments of the 1H and 13C resonances of 40-epi-(N1-tetrazolyl)-rapamycin and revised 13C assignments for rapamycin. Magn. Reson. Chem. 2005, 43(2), 174-175.

6. Schuler W., Sedrani R., Cottens S. et al. SDZ RAD, a new rapamycin derivative, pharmacological properties in vitro and in vivo. Transplantation, 1997, 64, 36-42.

7. Schuurman H.J., Cottens S., Fuchs S. et al. SDZ RAD, a new rapamycin derivative, synergism with cyclosporine. Transplantation, 1997, 64, 32-35.

8. Karyekar C.S., Pradhan R.S., Freeney T. et al. A phase I multiple-dose escalation study characterizing pharmacokinetics and safety of ABT-578 in healthy subjects. J. Clin. Pharmacol., 2005, 45(8), 910-918.

9. Buellesfeld L., Grube E. ABT-578-eluting stents. The promising successor of sirolimus- and paclitaxel-eluting stent concepts? Herz, 2004, 29(2), 167-170.
10. Modern Dictionary of Foreign Words. Moscow, «Russkiy yazyk», 1993. –740 pp.
11. Lemos P.A., Serruys P.W., Sousa J.E. Drug-eluting stents: cost versus clinical benefit. Circulation, 2003, 107(24), 3003-3007.
12. Armstrong J., Gunn J., Arnold N. et al. Angiopeptin-eluting stents: observations in human vessels and pig coronary arteries. J. Invasive. Cardiol., 2002, 14(5), 230-238.
13. Kwok O.H., Chow W.H., Law T.C. et al. First human experience with angiopeptin-eluting stent: A quantitative coronary angiography and three-dimensional intravascular ultrasound study. Catheter. Cardiovasc. Interv., 2005, 66(4), 541-546.
14. Sousa J.E., Serruys P.W., Costa M.A. New frontiers in cardiology: drug-eluting stents: Part II. Circulation, 2003, 107(18), 2383-2389.
15. Li C., Cantor W.J., Nili N. et al. Arterial repair after stenting and the effects of GM6001, a matrix metalloproteinase inhibitor. J. Am. Coll. Cardiol., 2002, 39(11), 1852-1858.
16. Lovdahl C., Thyberg J., Hultgardh-Nilsson A. The synthetic metalloproteinase inhibitor batimastat suppresses injury-induced phosphorylation of MAP kinase ERK1/ERK2 and phenotypic modification of arterial smooth muscle cells in vitro. J. Vasc. Res., 2000, 37(5), 345-354.
17. Araujo C.M., Rando G.A., Mauro M.F. et al. Batimastat-eluting stent implantation for the treatment of coronary artery disease: results of the Brazilian pilot study. Arq. Bras. Cardiol., 2005, 84(3), 256-260.
18. Geraldes P., Sirois M.G., Bernatchez P.N., Tanguay J.F. Estrogen regulation of endothelial and smooth muscle cell migration and proliferation. Role of p38 and p42/44 mitogen-activated protein kinase. Arterioscler. Thromb. Vasc. Biol., 2002, 22, 1589-1590.
19. Mushkambarov N.N., Kuznetsov S.L. Molecular Biology. – Moscow, Meditsinskoye Informatsionnoye agentstvo", 2003. –544 pp.
20. New G., Moses J.W, Roubin G.S. et al. Estrogen-eluting, phosphorylcholine-coated stent implantation is associated with reduced neointimal formation but no delay in vascular repair in a porcine coronary model. Catheter. Cardiovasc. Interv., 2002, 57(2), 266-271.
21. Abizaid A., Albertal M., Costa M.A. et al. First human experience with the 17-beta-estradiol-eluting stent: the Estrogen And Stents To Eliminate Restenosis (EASTER) trial. J. Am. Coll. Cardiol. 2004, 43(6), 1118-1121.
22. Mashkovskiy M.D.. Medicinal Agents. Manual for Physicians.- Moscow, "Novaya Volna", 2002, in 2 vol. Vol.2, 608 pp.
23. Serruys P.W., Ormiston J.A., Sianos G. et al. ACTION investigators. Actinomycin-eluting stent for coronary revascularization: a randomized feasibility and safety study: the ACTION trial. J. Am. Coll. Cardiol., 2004, 44(7), 1363-1367.
24. Crooke S.T. Progress in antisense technology. Annu. Rev. Med., 2004, 55, 61-95.
25. Kipshidze N.N., Kim H.S., Iversen P. et al. Intramural coronary delivery of advanced antisense oligonucleotides reduces neointimal formation in the porcine stent restenosis model. J. Am. Coll. Cardiol., 2002, 39(10), 1686-1691.
26. Kutryk M.J., Foley D.P., van den Brand M. et al. ITALICS Trial. Local intracoronary administration of antisense oligonucleotide against c-myc for the prevention of in-stent restenosis: results of the randomized investigation by the Thoraxcenter of antisense DNA using local delivery and IVUS after coronary stenting (ITALICS) trial. J. Am. Coll. Cardiol., 2002, 39(2), 281-287.
27. Sousa J.E., Serruys P.W., Costa M.A. New frontiers in cardiology: drug-eluting stents: Part I. Circulation., 2003b, 107(17), 2274-2289.
28. Abizaid A., Albertal M., Ormiston J. et al. Impact trial: Angiographic and intravascular ultrasound observations of the first human experience with mycophenolic acid-eluting polymer stent system. Catheter. Cardiovasc. Interv., 2005, 66(4), 491-495.
29. Grewe P.H., Deneke T., Holt S.K. et al. Scanning electron microscopic analysis of vessel wall reactions after coronary stenting. Z. Kardiol., 2000, 89(1), 21-27.
30. Rogers C., Parikh S., Seifert P. et al., Endogenous cell seeding: remnant endothelium after stenting after stenting enhances vascular repair. Circulation, 1996, 94, 2909-2914.
31. Kong D., Melo L.G., Mangi A.A. et al. Enhanced inhibition of neointimal hyperplasia by genetically engineered endothelial progenitor cells. Circulation, 2004, 109(14), 1769-1775.
32. Aicher A., Heeschen C., Mildner-Rihm C. et al. Essential role of endothelial nitric oxide synthase for mobilization of stem and progenitor cells. Nat. Med. 2003, 9(11), 1370-1376.
33. Asahara T., Murohara T., Sullivan A. et al. Isolation of putative progenitor endothelial cells for angiogenesis. Science, 1997, 275(5302), 964-967.
34. Werner N., Junk S., Laufs U. et al. Intravenous transfusion of endothelial progenitor cells reduces neointima formation after vascular injury. Circ. Res., 2003, 93(2), e17-24.
35. Aoki J., Serruys P.W., van Beusekom H. et al. Endothelial progenitor cell capture by stents coated with antibody against CD34: the HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man) Registry. J. Am. Coll. Cardiol., 2005, 45(10), 1574-1579.
36. Walter D.H., Rittig K., Bahlmann F.H. et al. Statin therapy accelerates reendothelialization: a novel effect involving mobilization and incorporation of bone marrow-derived endothelial progenitor cells. Circulation, 2002, 105(25), 3017-3024.
37. Jaschke B., Michaelis C., Milz S. et al. Local statin therapy differentially interferes with smooth muscle and endothelial cell proliferation and reduces neointima on a drug-eluting stent platform. Cardiovasc. Res. 2005, 68(3), 483-492.

Clinical Outcome of Endovascular Recanalization of Chronic Coronary Artery Occlusion

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Introduction: according to the prognoses, by the year of 2020 cardiovascular diseases will account for about 36% of all deaths. Among these, CAD plays a major role and its treatment is of highest social and economic importance, equal to the most crucial challenges of the society (1). Annual mortality rate due to CAD ranges from 5.4% to 11.3% and is largely dependent on the severity of coronary artery lesions and myocardial function. Thus, stenosis of a single coronary artery is associated with 1.6 to 6.6% mortality, stenosis of two arteries - 6.4 to 13.7% mortality, stenosis of three arteries - 9-16.7% mortality.

Completely obstructed arteries, i.e. occlusions represent an important share of coronary lesions in CAD; they are found in 15 - 40% patients at coronary angiography, whereas the endovascular interventions preformed for such condition currently account for 10-20% of all interventional procedures (5). Patients with chronic occlusions of the coronary arteries form the most severely affected group as compared to patients with stenotic vascular lesions without occlusions. They tend to have more severe angina and more frequent multiple lesions of coronary arteries; because of the more frequent history of myocardial infarction, left ventricular function in such patients is more severely compromised, than in patients with stenoses. (3, 6)

The rate of successful recanalization of chronic occlusions of coronary arteries during endovascular procedures ranges from 60 to 90% according to various authors (1, 2). Poor long-term outcome, i.e. restenosis, following endovascular interventions procedures performed for coronary artery occlusion, is significantly more common, than in patients without occlusion (4, 12). In addition, the majority of patients had myocardial infarction in the territory of this artery and, consequently, have scar changes in corresponding myocardial segments requiring substantially smaller amount of blood as compared to intact myocardium (17). With this, chronic coronary artery occlusion leads to the development of collateral perfusion in this artery's pool, which, to some extent, compensates the impaired blood supply (19, 20). These are the reasons for uncertainty as to the need for complicated and expensive endovascular therapy of coronary occlusions associated with a risk of severe complications. Nevertheless, interventional cardiologists are still performing procedures for coronary occlusions despite the fact, that there's no unambiguous answer on the question of when one should strive for recanalization and when there's no such need? This became the ground for the study, aimed at the evaluation of clinical pattern and left ventricular function after antegrade blood flow restoration in chronically occluded coronary arteries.

Purposes of study: to assess the long-term changes of clinical course and left ventricular function depending on the state of coronary bed after PTCA of chronic total coronary occlusions in CAD patients.

Patients and methods

The study enrolled 135 CAD patients, who underwent successful mechanical recanalization of chronic (over 3 months) total coronary occlusions between 1999 and 2005 in the Moscow City Center of Interventional Cardioangiology. The success rate was 95.9%. Patients with acute or recent (within 3 months) total coronary occlusions were excluded. Reperfusion procedure for chronic coronary occlusions consisted of mechanical recanalization with simultaneous PTCA and, in certain patients, stenting (70.4%). The age of occlusion was mostly assessed by the date of myocardial infarction in the territory of occluded artery or by the onset of most severe and prolonged chest pain episode, which differed from regular angina in every single patient. Occlusion duration was 3 to 6 months in 72.8% of patients, 6 to 12 months – in 18.8% of patients, over 1 year – in 8.4% of patients.

Table 1. Demographic and clinical data (n = 135).

Age (years)	54.58±7.1
Men	116 (85.9%)
MI history	122(90.4%)
Hypertension	92(68.1%)
Type 2 diabetes mellitus	13(9.6%)
Hypercholesterolemia	85(62.9%)
Smoking	98(72.6%)

Patients were mostly men with a history of MI confirmed clinically. All endovascular procedures were elective and one-staged, they were performed immediately after coronary angiography. In the long-term follow-up (mean at 6.9±2.6 months) the patients underwent a control examination, including coronary angiography.

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Preoperative NYHA angina class distribution was as follows: 5.2% of patients were in class I , 23.0% in class II, 64,4% - in class III, and 7,4% of patients - in class IV.

Nine (6.7%) patients had gastric or duodenal ulcer in remission, 3 (2.2%) patients – chronic pyelonephritis, 13 (9.6%) patients – type 2 diabetes mellitus, 3 (2.2%) patients – history of stroke.

As a rule, the patients were discharged at day 2 postoperatively with routine administration of 125 mg aspirin daily and, at least, 1-month cycle of ticlopidine 500 mg daily or clopidogrel 75 mg daily. In addition, symptomatic medical therapy was continued when necessary. Most commonly the patients had LAD occlusion (52.6%), second most common lesion was RCA occlusion (24.5%). Occlusions were mostly located in proximal (45.8%) or middle (48.3%) segments of coronary arteries. Eight patients had chronic total occlusion of 2 coronary arteries, successful recanalization of both arteries was performed in 3 of these patients. Multivessel stenoses were found in 68 (50.3%). Mean number of coronary arteries affected was 1.25±0.4. As stated above, the study was principally aimed at the long-term angiographic results of the procedure, therefore, all patients were divided between the following groups:

1) patients with preserved antegrade perfusion in the long-term follow-up after recanalization (TIMI II – III) (n =110).
2) patients with reocclusion after recanalization (TIMI 0) (n = 33).

Clinical examination included:

1. History analysis.
2. ECG.
3. Bicycle ergometry with stepwise increase of stress to reveal ischemic myocardial changes.
4. Selective coronary angiography and left ventriculography were performed according to the established procedure. Global and segmental contractile function, as well as the volumes of the left ventricle, were analyzed using DIMOL IK 9.133 software (2). To assess the contractile function of certain left ventricular segments depending on the corresponding artery, LAD was attributed to segments 1, 2 and 3, whereas CLx – to segments 4 and 5.

The study included only patients with successful mechanical recanalization, PTCA and/or stenting and TIMI 3 antegrade flow immediately after the procedure. Primary inclusion criterion was the follow-up examination at least within 6 months postoperatively, which included follow-up selective coronary angiography.

Statistical analysis was performed using Russian version of SPSS for Windows 10.0.5.

Study results.

Complete myocardial revascularization was achieved in 96 (71.1%) patients. In 95 patients recanalization and angioplasty of chronic total coronary occlusion was followed by implantation of 103 coronary stents, 40 patients underwent only balloon angioplasty. Six (5.8%) patients underwent implantation of 2 stents, another patient (1.05%) had 3 stents implanted into previously occluded artery.

Table 2. Stents implanted into coronary arteries.

Stents	Number
Matrix stents: 7	
Multilink Duet	1
Angiostent C1	3
Crown	2
MiniCrown	1
Module stents: 71	
Multilink Tetra	11
BX Sonic	23
Multilink Penta	3
BX Velocity	19
Biodivysio	9
R -stent	4
Cypher	2
Wire stents: 25	
Angiostent	5
Tenax	3
AVE	2
Cross FLEX	13
V -flex	2
Total:	103

Over 20% residual stenosis was found in 4 (2.9 %) patients in stenting group vs 6 (15%) patients in PTCA group ($p < 0.05$). Type A or B (AHA/ACC) intimal dissection was observed in 2 (2.4%) patients from stenting group vs 9 (22.5%) patients in PTCA group ($p<0.01$). There were no significant stenoses in these patients.

In 79 (58.5%) patients basic recanalization and PTCA for coronary occlusion were accompanied by endovascular procedures in other coronary arteries.

Complications: the following complications were encountered during recanalization of chronic coronary occlusions: threatening intimal dissection of proximal stump necessitating additional stenting in 3 (2.2 %) cases, acute occlusion of a large side branch in 1 (0.7%) case and ventricular fibrillation in 1 (0.7%) case. After the procedure virtually all patients had uneventful recovery, except one patient (0.7%) with coronary occlusion at the site of PTCA necessitating repeated recanalization and PTCA.

Late changes in the artery.

All 135 patients underwent follow-up coronary angiography and ventriculography at 6.9±2.6 months postoperatively.

Antegrade TIMI 3 flow persisted in 110 (76.9 %) patients, of these 52 patients (36.4%) had restenosis of various degree. Reocclusion (TIMI 0 – 1) occurred in 33 (23.5%) patients ($p< 0.05$). See Fig. 1.

Analysis of restenosis and reocclusion incidence in certain coronary arteries showed no significant difference.

Table 2. Long-term outcome of recanalization
$p<0.002$

The table shows, that stenting ensures good long-term outcome significantly more commonly and reoc-

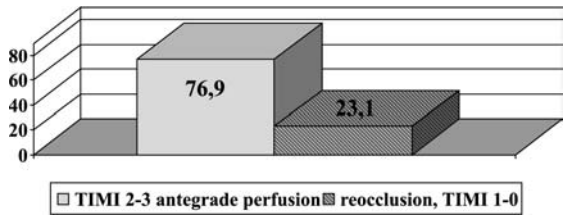


Fig. 1. Long-term changes of functional state of coronary arteries.

clusion was significantly more seldom as compared to

Outcome	Stenting (%)	PTCA (%)
No restenosis	45 (43.7%)	13 (32.5%)
Restenosis	37 (35.9%)	15 (37.5%)
Reocclusion	21 (20.5%)	12 (30.0%)

PTCA.

Analysis of potential predictors of coronary restenosis and reocclusion after recanalization showed, that well-developed collateral pathways to the territory of occluded artery were significantly more common in patients with restenosis or reocclusion ($p < 0.05$). Multifactorial analysis revealed significant correlation ($p < 0.05$) between long-term restenosis or reocclusion on one hand and left ventricular dilation and presence of collateral pathways to the occluded artery on the other hand.

The type of lesion, the time and length of occlusion, stump shape, baseline arterial diameter, the presence of adjacent large side branches, severe calcification and other factors had no influence on the rate of restenosis and reocclusion in this study.

Global contractile function of left ventricular myocardium in study groups. Analysis of global contractile function was performed using end-systolic and end-diastolic volumes, as well as the left ventricular ejection fraction. There was a significant long-term increase of ejection fraction as compared to baseline values from 56.29±1.35 to 59.76±1.34 on average ($p< 0.02$). Such increase of LVEF was due to patients with preserved long-term antegrade perfusion in arteries at the site of recanalization or PTCA irrespective of the presence of restenosis. Reocclusion revealed no significant increase in LVEF. See Fig. 2

Comparison between preoperative and long-term end-diastolic and end-systolic LV volumes after recanalization of chronic occlusion showed, that patients with restored and preserved long-term antegrade perfusion had significant decrease of end-systolic LV volume from 71.9±3.1 ml to 63.9±2.4 ml on average ($p < 0.05$), whereas there were no significant changes of end-diastolic volume (see Figs. 3 and 4).

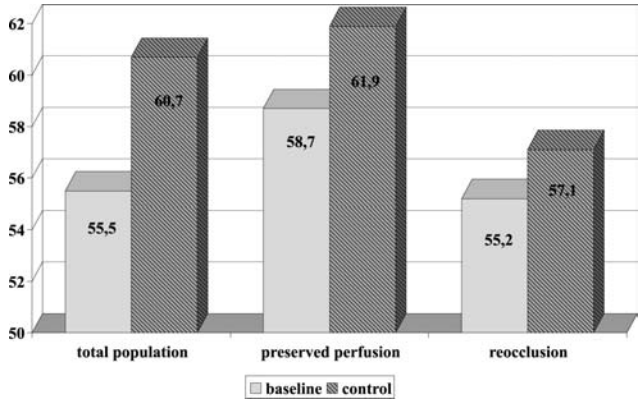
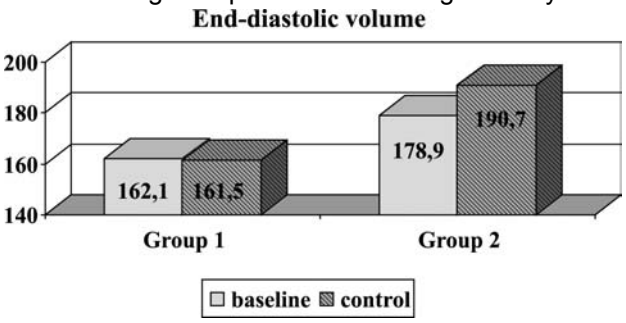


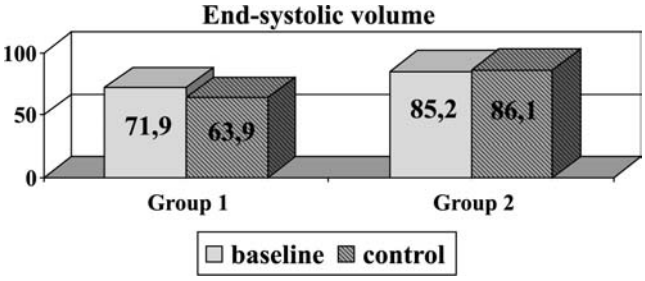
Fig. 2. Changes of LVEF in the study group.

Fig. 3. Long-term changes of end-diastolic LV volume in study patients.
Fig. 4. Changes of end-systolic LV volume depending on the long-term outcome of recanalization.

It is of interest, that baseline values of end-diastolic and end-systolic LV volumes in patients with preserved antegrade perfusion were significantly lower,



than in patients with reocclusion in the long-term period. Correspondingly, impaired LV contractile function and its dilation could be risk factor for repeated reocclusion after angioplasty. In addition, patients with reocclusion had non-significant increase of end-diastolic volume from 178.9±10.42 ml to 190.7±10.31 ml ($p = 0.2$). End-systolic LV volume was practically unchanged.



We assessed changes of myocardial contractile function in ventricular segments receiving blood from the occluded arteries. The study showed, that the preserved effect of the procedure in the long-term period in LAD correlated with improved contractile function of anterolateral and apical regions. Similar pattern was found for total contractile function of the above regions of the left ventricle. See Tables 4 and 5.

There were no significant changes of segmental contraction in LAD territory in patients with reocclusion either by length or by area.

Patients with preserved antegrade perfusion in RCA had significant increase of diaphragmatic contractile function both by length (from 11.42±4.5 to 21.25±4.9 ($p < 0.02$)), and by area (from 27.0±2.8 to 37.12±3.6 ($p < 0.05$)). Patients with RCA reocclusion had no significant change of contractile function of this territory. See Tables 6 and 7.

Table 6. Changes of LV myocardial contractile function in RCA territory in patients with preserved antegrade perfusion.

Table 4. Changes of LV myocardial contractile function in LAD territory in patients with preserved antegrade perfusion.

		Segments		
		anterobasal	anterolateral	Apical
length	Baseline	42,46±4,6	21,9±3,3	7,92±2,7
	Control	43,82±4,1	29,06±3,1	14,23±3,2
area	Baseline	57,61±4,6	37,88±3,3	24,49±3,5
	Control	61,08±5,0	47,67±4,3	33,51±3,8

Table 7. Changes of LV myocardial contractile function in RCA territory

Table 5. Changes of LV myocardial contractile function in LAD territory in patients with reocclusion.

		Segments		
		anterobasal	anterolateral	Apical
length	Baseline	38.43±8.7	18.86±7.3	6.57±6.1
	Control	43.25±9.2	23.13±9.1	6.88±6.4
area	Baseline	57.43±6.9	31.57±7.8	22.56±4.2
	Control	62.29±7.5	42.57±8.1	26.29±4.7

in patients with reocclusion.

Analysis of LV contractile function in LCx territory in patients with preserved antegrade perfusion showed significant increase of diaphragmatic segment contraction only by area (from 27.0±2.8 at baseline to

		Segments	
		Diaphragmatic	Lower basal
length	Baseline	11,42±4,5	21,08±2,8
	Control	21,25±4,9	25,31±3,2
area	Baseline	22,58±4,3	36,08±3,6
	Control	36,27±4,1	38,23±3,5

37.12±3.6 at follow-up ($p < 0.05$)). There were no significant increase in other contractility parameters. This

		Segments	
		Diaphragmatic	Lower basal
length	Baseline	10.0±8.3	14.14±8.8
	Control	18.25±10.1	12.89±8.1
area	Baseline	16.7±9.7	23.86±7.6
	Control	24.5±10.5	24.5±8.4

could be due to the fact, that these regions of the left ventricle, as a rule, receive blood from both LCx and RCA. Analysis of long-term changes of contractile function in LCx territory in patients with reocclusion showed no significant change in either of the above parameters. See Tables 8 and 9.

Therefore, the study provided strong evidence of the fact, that the long-term improvement of LV function after recanalization of chronic total coronary occlusions is mostly due to the increase of function in those myocardial segments, which receive blood from these arteries, provided that antegrade perfusion is preserved.

Clinical pattern of angina in the long-term period

During the assessment of clinical pattern in patients in the long-term period after recanalization of

Table 8. Changes of LV myocardial contractile function in LCx territory in patients with preserved antegrade perfusion.

		Segments	
		Apical	Diaphragmatic
length	Baseline	19.18±2.8	18.82±2.2
	Control	19.44±2.7	21.2±2.5
area	Baseline	34.36±3.1	27.0±2.8
	Control	37.32±3.0	37.12±3.6

Table 9. Changes of LV myocardial contractile function in LCx territory in patients with reocclusion.

		Segments	
		Apical	Diaphragmatic
length	Baseline	16.25±2.9	9.25±2.3
	Control	18.25±2.8	10.20±2.6
area	Baseline	28.25±4.5	18.25±4.2
	Control	30.0±4.8	17.0±3.9

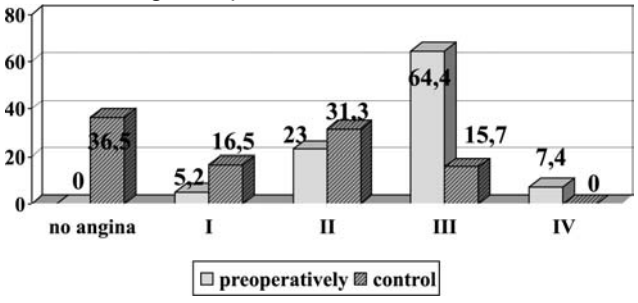
chronic coronary occlusions attention was mostly paid to the presence or absence of angina episodes per se, as well as to the changes of angina class. In addition, the results of exercise testing, i.e. the presence of pain or ECG changes suggesting transient myocardial ischemia, were taken into account.

The study provided strong evidence of the fact, that recanalization of coronary occlusion provided that the effect is preserved in the long-term period, has a positive effect on the clinical pattern. Thus, long-term follow-up examination revealed no angina episodes in one third of patients, who had at least class I angina at baseline. In addition, the number of class I or II angina patients increased and the number of class III or IV angina decreased (see Fig. 5).

Fig. 5. Changes of angina class in general population of patients.

Interestingly, 89.6% of patients were taking antianginal agents preoperatively, whereas in the long term period only 57.8% were in need of such drugs ($p< 0.01$).

In general, positive changes in clinical presentation of angina were detected in 86.0% of patients with preserved antegrade perfusion, whereas in reocclusion



group only 56.2% had such improvement ($p< 0.01$).

Table 10. Time to angina recurrence. $P< 0.01$

As stated above, 36.5% of patients had no episodes of angina in the long-term period, most of them had preserved effect of endovascular procedure. In the majority of patients with recurrent angina the recurrence was within 1 to 3 months. Obviously, this

coincided with the time, when restenosis and/or reocclusion develops after recanalization. In addition, some patients with reocclusion (10.2 %) had no recurrent angina. This emphasizes the advisability of repeated coronary angiography despite the absence of recurrent angina in order to reveal restenosis or reocclusion to be repaired.

	No recurrence	<1 month	1-3	3-6	Over 6
Without reocclu-	53 (49.53 %)	8 (7.5 %)	27	17	2 (1.9%)
With reocclusion	3 (9.7 %)	3(9.7 %)	17	8 (25.8%)	0

Comparison of long-term bicycle ergometry results

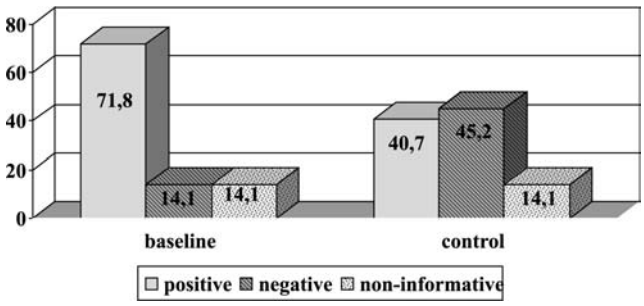
Comparison of long-term bicycle ergometry results at follow-up showed, that general population of patients had significant decrease of positive and increase of negative test results ($P < 0.05$). In general, such positive changes are found in patients with preserved effect of endovascular procedures.

See Fig. 6 and Table 10.

Fig. 6. Comparison of bicycle ergometry results.

Table 11. Comparison of the number of negative stress-tests and the long-term outcome of endovascular procedures.

The table shows, that negative results of bicycle ergometry were found in 41 (67.2%) patients without reocclusion vs 5 (8.2%) patients with reocclusion ($P < 0.05$.)



Therapeutic strategy after follow-up coronary angiography

After follow-up coronary angiography the patients with good long-term outcome of prior endovascular procedure were recommended to continue through symptomatic therapy and outpatient cardiological follow-up. Medical therapy included routine disaggregants (aspirin 125 mg daily or trombo-ass 100 mg daily). Patients with long-term restenosis or reocclusion underwent 39 (52.7% of patients in the group) PTCA procedures and 2 (2.7%) stenting procedures. In 6 patients (8.1%) repeated recanalization and PTCA was ineffective, as well as in 13 patients (17.6%) with lesions in other coronary arteries, therefore, they were recommended direct myocardial revascularization.

	Baseline	Control
Without reocclusion	10 (16.4%)	41 (67.2%)
With reocclusion	4 (6.6%)	5 (8.2%)

CONCLUSION

This study had driven us to conclusion, that in the majority of patients (72%)* endovascular procedures ensured restoration of antegrade perfusion in chronic total coronary occlusions. The rate of complications is around 3 – 4%. In most patients (76.9 %) the effect of antegrade reperfusion persisted for at least 6 months postoperatively, at the same time, 36.4% of patients had restenosis and 23.1% of patients - reocclusion. Good long-term outcome after stenting was significantly more common and the rate of reocclusion significantly less common as compared to PTCA.

In the majority of patients (86%) after reperfusion of chronic total coronary occlusion angina episodes were completely or substantially reduced and the exercise tolerance increased.

Global and regional LV contractile function was improved after reperfusion of chronic total coronary occlusion. This effect was detected only with preserved antegrade perfusion in the long-term period after endovascular procedures. In patients with reocclusion no substantial long-term improvement of LV function was observed.

Risk factors increasing the rate of long-term restenosis and reocclusion after coronary recanalization and angioplasty are: dilated LV chamber and well-developed collateral pathways to the occluded artery at baseline.

* - results from Moscow City Center of Interventional Cardioangiology

References:

1. D.G. Ioseliani. Important issues of cardiology. Moscow, 2002: p. 3.

2. D.G. Ioseliani, Ye.P. Velikhov, V.G. Gnedenko, Ye.M. Faynberg. Informational and communicational technology in iterventional cardiology and radiology. International Journal of Interventional Cardioangiology, 2005, V. 8: p. 48

3. A.P. Savchenko, N.I. Abdullin, Yu.G. Matchin et al. Clinical pattern and angiographic sings of chronic total coronary occlusion. Bulletin of roentgenology and radiology, 2000, V. 4: p. 4-10.

4. Cavallini C. Clinical, angiographic, and procedure factors predicting coronary restenosis after stent implantation: synthesis of the evidence. Ital. Heart J, 2001, 2 (7 Suppl), 719-32.

5. Danchin N., Angioi M., Rodriguez R.M. Angioplasty in chronic coronary occlusion. Arch. Mal. Coeur Vaiss., 1999, 92(11 Suppl), 1657-60.

6. Delacretaz E., Meier B. Therapeutic Strategy With Total Coronary Artery Occlusions. Am. J. Cardiol., 1997, 79, 185-187.

7. Dharmadhikari A.V., Airoldi F.M., Sheiban I.V., Tzifos V.T. Percutaneous Revascularisation in Patients with Poor Left Ventricular Function: Procedural and Mid-term Results. J. Am. Coll. Cardiol., 2002, 39, 313B.

8. Dong S., Jeong M., ClioJ. etal. Stenting versus non-stenting after revascularization of chronic total coronary artery occlusion: short- and long- term clinical and angiographic results. Chin. Med. J. (Engl), 2000, 113(3), 222-4.
9. Jacob S., Ghobrial M., Albornoz AM., et al. Coronary Artery Lesion Site and Predilection for Restenosis: A Retrospective Analysis. J. Am. Coll. Cardiol., 2002, 39, 307B.
10. Lotan C., Rozenman Y., Hendler A. et al. Stents in total occlusion for restenosis prevention. The multicentre randomized STOP study. The Israeli Working Group for Interventional Cardiology. Eur. Heart J., 2000, 21(23), 1960-6.
11. Meier B. Chronic total occlusion: how do we get there from here? J. Invasive Cardiol., 2001,13 (3), 233-5; discussion 262-4.
12. Olivari Z., Piscione F., Rubartelli P., et al. Percutaneous Coronary Interventions of Chronic Total Occlusions (CTO): Impact of Successful Procedures on One Year Clinical Outcome in Patients With Single and Multivessel Disease. J. Am. Coll. Cardiol., 2002, 39, 16B.
13. Piscione F., Galasso G., Maione A.G. et al. Immediate and long-term outcome of recanalization of chronic total coronary occlusions. J. Interv. Cardiol., 2002, 15(3), 173-9.
14. Rubartelli P., Niccoli L., Verna E. et al. Stent Implantation Versus Balloon Angioplasty in Chronic Coronary Occlusions: Results From the GISSOC Trial. J. Am. Coll. Cardiol., 1998, 32, 90-6.
15. Sallam M., Spanos V., Briguori C. et al. Predictors of re-occlusion after successful recanalization of chronic total occlusion. J. Invasive Cardiol., 2001, 13(7), 511-5.
16. Sirnes A., Golf S., Myreng Y. et al. Stenting in Chronic Coronary Occlusion (SICCO): A Randomized, Controlled Trial of Adding Stent Implantation After Successful Angioplasty. J. Am. Coll. Cardiol., 1996, 28, 1444-51.
17. Van Belle E., Blouard Ph., McFadden E., Lablanche J-M et al. Effects of stenting of recent or chronic coronary occlusion on late vessel patency and left ventricular function. Am. J. Cardiol., 1997, 80, 1150-1154.
18. Werner G.S., Ferrari M., Betge S. et al. Collateral function in chronic total coronary occlusions is related to regional myocardial function and duration of occlusion. Circulation, 2000, 104 (23), 2784-90.
19. Werner G., Richartz B., Gastmann O. et al. Immediate Changes of Collateral Function After Successful Recanalization of Chronic Total Coronary Occlusions. Circulation, 2000, 102,250.

Pre-Hospital Thrombolytic Therapy for Acute Q-Wave Myocardial Infarction in Emergency Coronary Care and Intensive Care

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Introduction

Q-wave myocardial infarction is a consequence of total occlusion of a coronary artery supplying the infarction and peri-infarction areas.

Reperfusion of the infarct-related artery substantially decreases the rate of complications and results in significant reduction of mortality in this severe condition. Multiple studies has provided strong evidence, that systemic thrombolysis in patients with Q-wave MI, which contributes to reperfusion of the infarct-related artery, provides 18 to 26% decrease in hospital mortality. Particular role is reserved for the time from the onset of symptoms to the institution of systemic thrombolysis. Early thrombolytic therapy (ETT) has a positive effect on myocardial electric stability, prevents hemodynamic complications, contributes to the most favorable remodeling of the left ventricle, thus decreasing the incidence of disability.

Reduction of TLT time to 2 hours from the onset of symptoms increases the efficacy of reperfusion by 38%. With this stroke volume significantly rises and the hospital mortality rate becomes substantially lower, than the mean statistical value.

Obviously, emergency care team is the first to arrive to the patient within the first hours of the disease. Thus, in Moscow, acute myocardial infarction is diagnosed within the first 6 hours by emergency care teams in over 50% of cases.

A very important conclusion relates to safety of medical reperfusion using pre-hospital TLT provided that the indications and contraindications are well defined.

In about 50% of patients with Q-wave acute myocardial infarction, who received emergency care, the chest pain episode had developed within 6 hours prior to arrival of the emergency team, therefore, these patients are potential candidates for TLT.

Diagnosis of acute Q-wave myocardial infarction

Timely and proper diagnosis of Q-wave MI to a great extent contributes to the early beginning of therapy and prevention of severe complications. Apart of a characteristic pain (retrosternal pain over 20 min in duration resistant to nitrates) suggesting ACS, a major diagnostic tool is the electrocardiography. Criteria of a Q-wave MI include:

* over 2 mV ST elevation in two or more adjacent leads (see Fig. 1a); for inferior myocardial infarction – in at least two of the leads II, III, aVF (see Fig. 1b);
* acute left bundle branch block (LBBB) accompanied by a characteristic pain episode; it ought be reminded, that the longevity of LBBB can be assessed only in comparison with recent ECG records of the patient.

Fig.1a. ECG in a patient with Q-wave anteroapical LV myocardial infarction

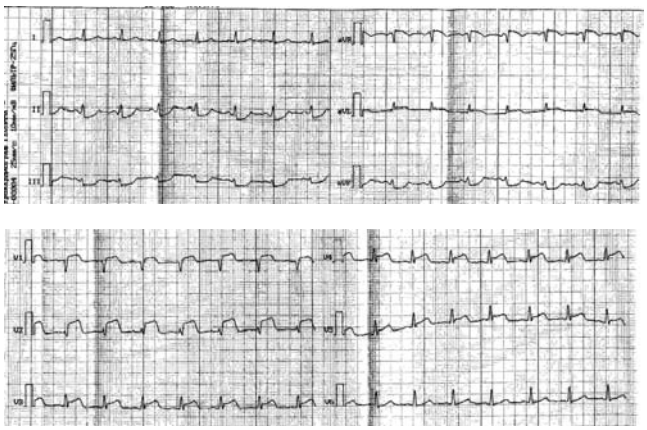
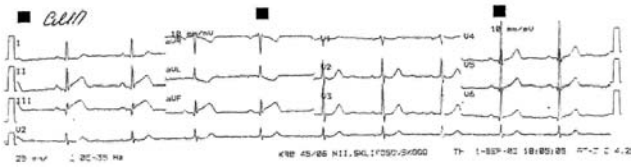


Fig.1b. ECG in a patient with Q-wave inferior LV myocardial infarction



Indications to pre-hospital TLT

An indication to pre-hospital thrombolytic therapy is the acute Q-wave myocardial infarction within the first 6 hours after the onset of symptoms.

Later use of TLT is not reasonable, as the likelihood of reperfusion becomes increasingly poor after the 6-hour threshold, in addition, the rate of post-reperfusion myocardial injury is high.

Contraindications:

There are absolute and relative contraindications to TLT.

Absolute contraindications include:

* Acute internal bleeding

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* Recent (within the last 10 days) severe gastrointestinal hemorrhage or urinary tract bleeding
* Recent (within the last 10 days) major surgery or injury to the internal organs (e.g., in patients after cardiopulmonary resuscitation) or biopsy of the internal organs
* Recent (within the last 2 months) brain/spinal trauma or surgery
* Hemorrhagic diathesis, including thrombocytopenia
* History of hemorrhagic stroke, neurological deficit
* Suspected aortic dissection or acute pancreatitis
* Pregnancy and delivery
* Repeated administration of streptokinase within 2 years after the first administration

Relative contraindications mostly include conditions inducing creating risk of bleeding:

* severe hepatic or renal disease
* cerebrovascular disease
* brain/spinal injury or surgery
* history of gastrointestinal or urinary bleeding
* uncontrolled hypertension (BP above 180/120 mm Hg)
* deep venous thrombosis of the lower limbs
* cardiac thrombus
* acute pericarditis or infectious endocarditis
* transient ischemic attacks within the last 6 months
* oral anticoagulant therapy
* recent traumatic cardiopulmonary resuscitation
* recent puncture of a vessel, not necessitating compression.

Relative contraindications require maximum caution and strong reasoning when TLT is considered. The search of any of the above factors necessitates thorough analysis of all circumstances and highest possible exactness in the assessment of risk/benefit ratio of the thrombolytic agent.

Elderly age is not a contraindication. However, in patients over 75 (particularly in women) the risk of hemorrhagic stroke is significantly higher, than in young patients. Therefore, disuse of pre-hospitalthrombolytic therapy in elderly patients is reasonable, when the time after the onset of symptoms is above 3 hours.

Acute heart failure (pulmonary edema, cardiogenic shock) is also not a contraindication to TLT. In contrast, hemodynamic disorders in acute myocardial infarction require a more aggressive administration of a thrombolytic agent, which is summarized in the corresponding section.

The procedure of pre-hospital TLT

When the diagnosis of acute Q-wave myocardial infarction is confirmed and pre-hospital TLT is considered, the coronary care team doctor should provide the following measures:

* The entire complex of therapy according to the Guidelines for emergency care in myocardial infarction (taking into account previously administered agents);
* IV nitrates (adjusted by hemodynamic parameters);
* Control of hypertension and tachycardia with IV beta-blockers;
* Patient's written consent for the procedure;
* Repeated ECG prior to TLT. This manipulation is required to reveal possible signs of spontaneous reperfusion, when TLT should be rejected. Signs of spontaneous reperfusion are defined as significant reduction of ST to isoline as compared to the first ECG or the occurrence of negative T-waves in leads, where elevated ST was recorded, however, these are not absolute, reliable or doubtless signs of reperfusion, as suggested by studies comparing clinical pattern, ECG and findings on selective coronary angiography;
* Bringing defibrillator to complete readiness;
* Whenever possible, transportation of patient immediately after TLT, as the time to hospital admission should be reduced to the minimum;
* Permanent monitoring of heart rhythm and general condition, control of BP from the onset of therapy to the arrival to CCU;
* Specify the following when filling in medical documents:
  - the time of TLT start and completion
  - name, dose and schedule of the thrombolytic agent administration.

Thrombolytic agents and ways of administration

The most common and easily available agent in emergency care is the indirect plasminogen activator – Streptokinase (Streptase). Its mechanism of action is based on degradation of fibrin and fibrinogen resulting in hypocoagulation and thrombolysis. The preparation is delivered in bottles of 7 500 000 U and 1 500 000 U. The drug should be dissolved in 200 ml 5% glucose or normal saline before use.

Complete dose of streptokinase – 1500000 U – can be administered according to different schedules:

А). 250 000 – 300 000 U IV bolus during 5 min, the remainder is injected IV during 40 to 60 min

Б). IV infusion of 1500000 U within 60 min

To prevent anaphylactic reactions 30-150 mg prednisolone can be administered.

Hemodynamic complications, such as cardiogenic shock or pulmonary edema require a more active schedule of streptokinase administration, when the IV bolus is increased to 500000 U, whereas the remaining dose is introduced as a 30-min. drop infusion within 30 min.

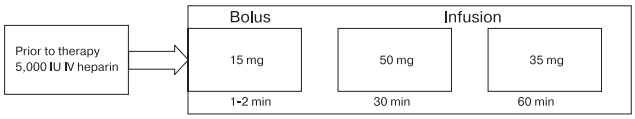
Tissue plasminogen activators (TPA) characterized by low activity in systemic circulation have become widely adopted during the last years. TPA is activated by direct contact with fibrin, causing degradation of

plasminogen to plasmin, which dissolves the thrombus. This pharmacological group includes Actilise (Boehringer Ingelheim, Germany). Its active substance – Alteplase – is a recombinant human tissue plasminogen activator. Major benefits of Actilise are the absence of systemic fibrinolysis and antigenic properties. The later makes the tissue plasminogen activator an agent of choice for repeated medical myocardial reperfusion.

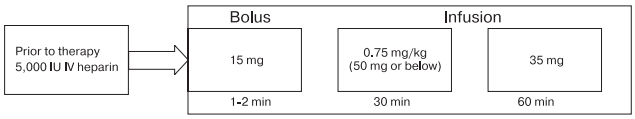
In addition, the efficacy of Actilise is preserved within 6 to 12 hours after the onset of symptoms.

The following schedules are used on the pre-hospital stage within the first 6 hours:

a) Body mass above 65 kg



b) Body mass below 65 kg



Complications and adverse effects of the thrombolytic therapy

Limited acceptance of systemic thrombolytic therapy in emergency care is largely due to the concept of risk of reperfusion rhythm disorders, bleeding or other complications.

Indeed, TLT can be accompanied by undesirable events both during administration and while in hospital. Major reactions include:

* Hemorrhagic complications
* Reperfusion rhythm disorders
* Anaphylactic reactions
* Hypotension

The analysis based on statistically significant large clinical experience of coronary care emergency teams of the Emergency Care Station of Moscow showed, that there were virtually no hemorrhagic complications at the pre-hospital stage, excluding 1 patient with gingival hemorrhage.

Few ventricular extrasystoles (2%) and as few as 2 cases of ventricular fibrillation can not be reliably identified as signs of reperfusion syndrome, as they are part of usual course of acute ischemic phase of a Q-wave myocardial infarction.

Most probably, the absence of hemorrhagic and reperfusion complications is due to short duration of pre-hospital stage, when these unfavorable events of TLT don't develop yet, consequently, taking all safety measures to prevent these complications during hospital stay is crucial.

Pre-hospital hypotension was observed almost in 21% of patients on streptokinase, however, this hypotension is transient and doesn't require medical correction, excluding temporary decrease of infusion rate. Most commonly, hypertension occurs after bolus injection of a thrombolytic agent.

Allergy is encountered in 1-2.5% of patients, anaphylaxis – in 0.1%. We have revealed 3 cases (0.3%) of allergy in the form of hives. Allergic signs necessitate immediate withdrawal of streptokinase and administration of hormones and antihistamines.

Assessment of TLT efficacy

The purpose of systemic thrombolysis for acute Q-wave myocardial infarction is known to be the reperfusion of the infarct-related artery (myocardial reperfusion). The criteria for assessment of TLT efficacy can be direct or indirect.

The most significant indirect ECG sign of myocardial reperfusion in MI patients are the speed and the degree of ST reduction towards isoline on serial ECG study.

The ECG presented below outline the efficacy of myocardial reperfusion.

In addition, ventricular rhythm disorders (even ventricular fibrillation) can suggest reperfusion of the infarct-related artery.

The problem of reocclusion

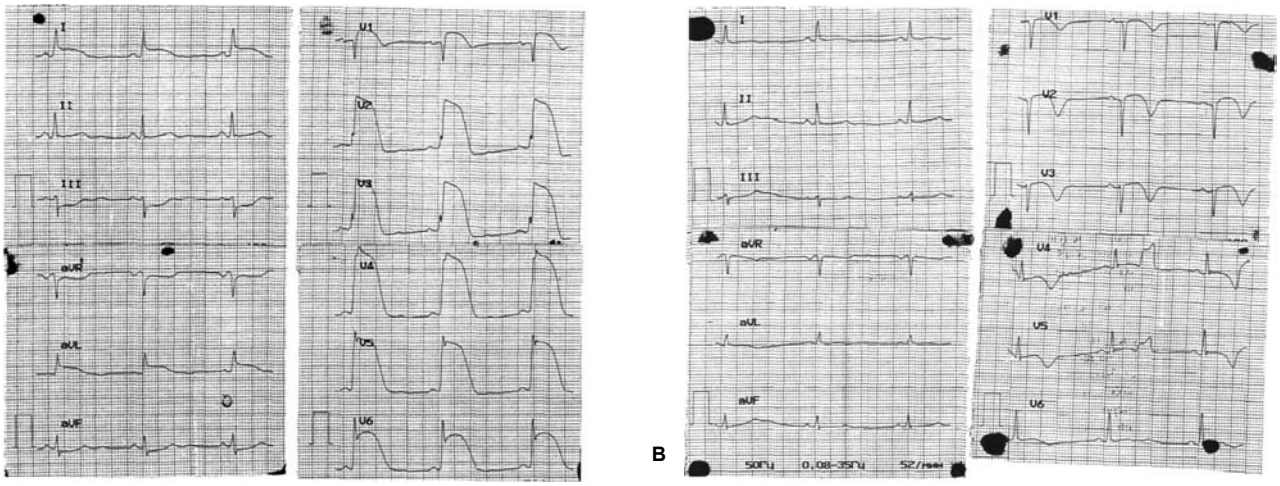


Fig. 2. ECG in Patient K., aged 49
a)1 hour after the onset
b) 1 hour after TLT completion

and the place for hospitalization

In the majority of cases, even successful TLT doesn't reduce the substrate for repeated coronary events. While dissolving the thrombus, it doesn't eliminate its major cause – the plaque narrowing the coronary artery. Successful early reperfusion is followed by high risk of repeated occlusion of the infarct-related artery, seriously complicating the clinical course of the disease. Therefore, timely endovascular procedures performed after reperfusion by systemic thrombolysis are crucial to prevent reocclusion.

TLT shall therefore be considered as the first pre-hospital stage of care in patients with MI. TLT must be performed as soon as possible after the onset of the disease by emergency care teams on pre-admission stage and followed by other up-to-date treatments in a specialized center aimed at reperfusion.

In this connection, admission to hospitals with twenty-four-hour interventional radiology service, is an important condition for optimal treatment of such patients. The decree of the Head physician of the Emergency Care Station is aimed at creation of continuity between these hospitals and the emergency teams and defines hospitals, where the MI patients after pre-hospital TLT should be admitted to.

Therefore, maximum early pre-hospital thrombolysis followed by complete reperfusion of coronary artery in hospital settings is an optimal up-to-date strategy in patients with acute Q-wave myocardial infarction.

REFERENCES

1. D.G. Iosseliani, I.S. Elkis, O.P. Soloviev et al. Combination of endovascular procedures and pre-hospital systemic thrombolysis in patients with acute myocardial infarction. Kardiologia, 2005, 3, 4-9.

2. D.G. Iosseliani, Ye.M. Fainberg et al. Computerized complex for automation of treatment and diagnosis in interventional cardiology. Abstracts of the 1-st Russian Meeting of Interventional Cardiologists. Moscow, 2002.

3. D.G. Iosseliani, A.A. Filatov et al. Transluminal balloon coronary angioplasty in patients with acute myocardial infarction. Kardiologia, 1995,. 6, 30.

4. F. Mille, V.M. Shkolnikov. Distribution of modern trends of mortality by the cause of death in Russia between 1965 and 1994. National Institute of Demographic Issues. Paris, 1996,140 p.

5. Yu.A. Ovasapian, I.S. Elkis. Guidelines for pre-hospital care in acute Q-wave myocardial infarction performed by emergency care teams of Moscow. Abstracts of the 3-rd Moscow Assembly «Zdorovie stolitsy». Moscow, 2004

6. R.G. Oganov, G.Ya. Maslennikova, S.A. Shalnova, A.D. Deyev. The role of cardiovascular and other non-infectious diseases in the health of Russian population. Propfilaktika i vossatnovlenie zdorovia, 2002, 2, 3

7. M.Ya. Ruda, I.I. Staroverov. B.N. Dorogun, Yu.A. Ovasapian et al. Thrombolytic therapy for acute myocardial infarction on pre-hospital and hospital stages. Kardiologia, 1990, 2.

8. I.S. Elkis, D.G. Iosseliani, V.A. Borisova, et al. Pre-hospital thrombolytic therapy for acute myocardial infarction. Abstracts of the 2-nd Moscow Assembly «Zdorovie stolitsy». Moscow, 2004

9. Ruda M.J., Staroverov I.I., Ovasapian Yu.A. et al. "Pre-hospital thrombolytic therapy in myocardial infarction patients". 12th Congress of the International Society on thrombosis and haemostasis. Japan, Tokio,1989.

Renal Angioplasty: Immediate and Long-Term Results

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INTRODUCTION

Impaired renal vascularization is the known cause of hypertension in certain patients. The incidence of renovascular hypertension among all forms of the disease is 2-3% (1, 3). The most common causes of renal ischemia are atherosclerotic stenosis or occlusion (75-80%), fibromuscular dysplasia (FMD) (15%), and aortoarteriitis (8-10%). Other causes are extremely rare (1, 2, 18). Atherosclerotic lesions of the renal arteries (RA) remain silent for a long period of time. Nevertheless, this process has progressive course and, according to various authors (4-6), leads to total RA occlusion 2-3 years after the disease is diagnosed clinically in one fifth of all patients. In addition to hypertension, hemodynamically significant RA stenosis associated with renal hypoperfusion results in renal failure and increased risk of other cardiovascular events (19).

Despite the fact, that the role of renal vascularization disorders in the pathogenesis of hypertension and renal failure is currently doubtless, many questions of diagnosis and treatment of this syndrome are still unclear. Indications to various treatment options for RA lesions are also not well established. These questions became particularly important after the introduction of endovascular methods for renal vessels reperfusion into clinical practice.

Some authors consider the balloon angioplasty of RA to be most effective for correction of stenosis due to FMD. Success rate of the procedure ranges from 82% to 100% (10, 11, 12, 13). In atherosclerotic stenosis stenting is more preferable. Immediate angiographic success of stenting approximates 100% (14-16, 8).

Assessment of the long-term results of endovascular RA repair showed, that the rate of re-stenosis after successful RA balloon angioplasty in FMD patients is around 10-11% vs 10% to 55% in atherosclerotic RA stenosis. Stenting is associated with substantially better results with restenosis rate ranging from 11 to 23% (39-43).

Analysis of 13 studies performed between 1989 and 1995 showed, that hypotensive effect of endovascular repair for FMD is encountered in 80-90% of cases vs 60-70% in atherosclerotic patients. Normalization of BP in FMD patients occurs in 50-55% of cases vs 10% or below in atherosclerotic lesions (see Table 1).

Table 1. Hypotensive effect of RA angioplasty/stenting in patients with atherosclerotic stenosis or FMD.

	FMD	Atherosclerosis
Hypotensive effect (%)	80-90	60-70
BP normalization (%)	50-55	10

(Data of Baert et al., 1990; Tegtmeyer et al., 1991; Cluzel et al., 1994; Lossino et al., 1994; Rodriguez et al., 1994; Bonelli et al., 1995; Jensen et al., 1995; Baumgartner et al., 1997; Klinge et al., 1989; Canzanello et al., 1989; Julien et al., 1989; Martin et al., 1992; Eldrup-Jorgensen, 1995).

Restoration of normal or nearly normal blood flow in RA, apart of hypotensive effect, is aimed at prevention of renal failure, which is the inevitable result of progression of atherosclerosis affecting normal renal function.

Analysis of 8 studies showed, that renal function, as measured by serum creatinine and/or creatinine clearance after RA angioplasty, is improved in 25-45%, remains stable in 10-30% and deteriorated in 10-35% of cases (Tekarski et al., 1993; Weibull et al., 1993; Dorros et al., 1995; Van de Ven et al., 1995; Henry et al., 1996; Blum et al., 1996; Boisclar et al., 1997; Taylor et al., 1997; Tullis et al., 1997).

Purpose of the study was to evaluate clinical and angiographic efficacy of RA angioplasty and stenting for hemodynamically significant stenosis.

CLINICAL FINDINGS AND ASSESSMENT OF PATIENTS

Between 1997 and December 2005 a total of 65 patients with RA stenosis underwent examination and treatment in Moscow City Center of Interventional Cardioangiology. The age of patients ranged from 34 to 73 years (mean age 58±8.78 years), suggesting preserved working capacity in the majority of patients.

All patients were hypertensive. Mean systolic BP was 155±16 mm Hg with maximum value of 220±29 mm Hg, mean diastolic BP was 91±9.3 mm Hg with maximum value of 120±18 mm Hg. History of hypertension was 1 to 30 years (mean 14.5±7.49 years). At baseline 48 patients were receiving hypotensive agents (71% of all patients). Good outcome was observed only in 9.5% of cases. The remaining 29% had no prior examination and treatment for hypertension.

The following comorbidities were encountered: CAD in 41 patients (63%), atherosclerosis of extracranial arteries in 20 patients (31%), Leriche's syndrome

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in 18 patients (28%), chronic renal disease (pyelonephritis, urolithiasis) in 17 patients (26%), diabetes mellitus in 10 patients (15%).

Twenty-two (22) patients (33.8%) had hypercholesterolemia, 14 patients (21.5%) had laboratory findings suggesting impaired renal function, which was significant in 2 (serum creatinine reaching 300 μmol/l) and moderate in 10 (serum creatinine 131 to 152 μmol/l) patients.

Contrast angiography showed stenosis of apparently atherosclerotic origin in 62 patients (95.4%) and stenosis due to FMD in 3 patients (4.6%). Unilateral RA lesions were found in 49 patients (75.4%), bilateral lesions – in 16 patients (24.6%), of which one female patient with double right RA had 3-vessel stenosis (two right and one left renal arteries). The stenosis was located in RA origin in 57 cases (70.4%), in the proximal segment – in 17 cases (21.0%), in the middle segment – in 6 cases (7.4%), and in one case (1.2%) the stenosis was located in the first-order branch of the left RA. Mean degree of stenosis prior to endovascular treatment was 77±9.2% (see Table 2).

Table 2. Angiographic findings in renal arteries.

TYPE OF LESION	Number	%
Atherosclerotic lesion	62	95.4
FMD	3	4.6
Unilateral RA stenosis	49	75.4
Bilateral RA stenosis	16	24.6
Stenosis at the RA origin	57	70.4
Stenosis of the proximal RA segment	17	21.0
Stenosis of the middle RA segment	6	7.4
Stenosis of the first-order RA branch	1	1.2
Stenosis degree		77±9.2

The following studies were performed to all patients before endovascular intervention: renal ultrasound study, BP monitoring, serum urea and creatinine measurement prior and immediately after the procedure, as well as on discharge; angiography. Low-osmolarity Omnipak-350 was used as a contrast medium.

Quantitative analysis of the angiographic findings was performed with Hicor unit (Siemens).

The advisability of renal reperfusion and the treatment option were chosen on the basis of complex estimation of examination results. We have used the following stents: Corinthian IQ (Cordis) – in 36 cases, Palmaz (Cordis) – in 8 cases, Bridge-X3 (Medtronic) – in 8 cases, Wallstent (Boston Scientific) – in 3 case.

Mean stent diameter was 6.6±1.76 mm, mean length - 17±1.76 mm.

Follow-up examination including angiography, was performed at 8+2.6 months (mean) in 33 patients. Eight (8) patients had follow-up period over 2 years.

RESULTS AND DISCUSSION

As a result of examination, 65 patients underwent 74 renal endovascular procedures: 19 balloon angioplasties vs 55 stenting procedures, of these direct stenting accounted for 30 cases.

All patients were observed in ICU during 4-5 hours following the endovascular procedure. They were monitored for BP, ECG and coagulation indexes. To prevent stent thrombosis and restenosis the patients received ticlopidine 500 mg daily or clopidogrel (plavix) 75 mg daily within 1 month following the procedure.

Optimal immediate angiographic outcome of balloon angioplasty was obtained in 18 cases (95%). Stenting was successful in 54 cases (98 %).

The immediate study results completely coincide with numerous published data (14,15,16,8).

All balloon angioplasty procedures were performed without complications. Stenting was complicated by RA occlusion due to dissection in one case (1.35%) and thrombosis of ileo-femoral arterial segment at the puncture side in one patient with severe iliac artery atherosclerosis (1.35%). On the whole, the rate of complications during endovascular RA repair was 2.7%. All complications were managed by open surgery. According to various authors, the rate of complications after balloon angioplasty and stenting of the renal arteries ranges from 2 to 10% (27-29). In 44 studies, which included 2993 patients with 2872 balloon angioplasty procedures and 792 stenting procedures, there were 515 complications, accounting for 17.2%, of these, 63 cases (2.1%) necessitated open surgery. The majority of complications were arterial spasm (2.64%) or dissection of the renal artery (2.44%). Complications due to dissection or thrombosis of the iliac arteries were observed in cases 10 (0.33%) (20-26). According to the published data, the mortality rate after angioplasty of renal arteries is 1-2% (30). There were no deaths in our study.

Therefore, the rate and the nature of complications observed in the study were same with those in other studies analyzed.

Immediate hypotensive effect was observed in all patients. In 75% of cases this effect was substantial, in 25% of cases there was a trend towards decreased BP due to maximum value with “working” blood pressure remaining stable. Mean volume of contrast medium utilized during the was 365+167 ml. Low-osmolarity contrast was used in all cases.

Hypotensive effect was preserved in the mid-term period in 67% of cases, recurrent hypertension was found in 33% of cases.

Clinical effect of RA angioplasty was assessed by renal function as well. Temporary impairment of the renal function immediately after the procedure followed by normalization within one week was observed in 16 patients (24.6%). Publications suggest that temporary impairment of renal function after angiography was due to contrast-induced nephropathy (CIN), which is found in 0.1 to 13% of patients (32). Most authors found the rate of CIN to be higher - 45% of all cases. Serum creatinine peaked at 3-5 days after contrast procedure and returned to normal range within 7-10 days (33-36). Risk factors for CIN are: renal failure at baseline, diabetes

mellitus, patient's dehydration due to diuretics, contrast medium volume over 125 ml, the use of high-osmolarity contrast (31, 32, 37, 38). Analysis of our study showed, that 9 patients (56%) with CIN had renal failure at baseline, 4 of these had type 2 diabetes mellitus.

Renal function impairment at 6-12 months as compared to initial level was found in 2 patients (6.0%), improvement was observed in 9 patients (27.3%), in 4 of them the renal function returned to normal range. In the remaining 22 patients (66.7%) the renal function remained stable. Particular attention was focused on CIN patients. Of these, 6 patients had follow-up examination. In 5 patients (83.3%) the renal function was found to be improved as compared to baseline. In one case the renal function decreased. Interestingly, renal function impairment was revealed in patients with coexisting renal disease (chronic pyelonephritis).

From the viewpoint of clinical efficacy, the results of endovascular treatment in our study coincide with the results of other authors. The absence of subsequent renal function impairment in the majority of patients is thought to be due to the fact, that baseline serum creatinine in the patients was below 300 μmol/l. Publications suggest, that ischemic nephropathy is found in patients with creatinine above 500 μmol/l. These authors believe, that the majority of these patients become dialysis-dependent approximately 6 months following stenting (17). Patient with serum creatinine below 133 μmol/l have minimum risk for renal function decrease (18).

Mid-term results of 8 RA balloon angioplasty procedures and 29 RA stenting procedures were assessed in 33 patients 6 to 12 months after the procedure. The rate of restenosis following angioplasty was 12.5% vs 10% after stenting. Two (2) patients (7%) had hemodynamically significant kinking of RA at the distal edge of stent deployed. This was successfully managed by endovascular repair (angioplasty or stenting).

The fate of 9 patients was followed for over 2 years postoperatively, including 6 patients after stenting and 3 patients after balloon angioplasty of RA. Mean follow-up was 3.63+0.07 years. Follow-up angiography showed restenosis in 1 case after stenting, angioplasty outcome was successful in all cases. Hypotensive effect was preserved in 67% of cases, renal function impairment was found in a single patient with restenosis. Other patients had unchanged renal function.

CONLCUSION

The study confirmed findings of other authors, suggesting the possibility of successful angioplasty without major complications and with good immediate outcome both in balloon angioplasty alone (95%) and in its combination with stenting (98%) in the majority of patients with RA stenosis. Immediately after successful angioplasty the majority of patients (75%) developed hypotensive effect, which persisted in the follow-up in about 67% of these patients. In addition, the effect of reperfusion is preserved in the long-term period (>2 years) in the majority of patients and the rate of restenosis after balloon angioplasty and stenting was 12.5% and 10%, respectively. In most cases of restenosis there is a possibility to successfully restore vessel lumen with balloon angioplasty. In no case did we found irreversible renal failure or the need for dialysis after angioplasty procedure. At the same time, none of the patients had baseline creatinine over 300 μmol/l. However, final conclusion on the efficacy of RA angioplasty for BP normalization and prevention of chronic renal failure in a large population of patients necessitates further experience.

REFERENCES

1. Arabidze G.G., Matveeva L.S., Kutzenko A.I. et al. Syndrome of malignant arterial hypertension (separate renal hemodynamics and rennin-angiotensin system). Proceedings of Soviet-American Symposium, 1978. M., Meditzina, 1980, 282.

2. Kniazev M.D., Krotovsky G.S. Surgical treatment of occlusive lesions of the renal arteries. Voronezh, Publishing house of Voronezh University, 1974, 149

3. Vaughan E.D., Carey R.M., Myers C.R. et al. Physiologic definition of blood pressure response to renal revascularization in patients with renovascular hypertension. Kidney, 1979, 9, 89-92.

4. Tullis M.J., Zierler R.E., Caps M.T. et al. Clinical evidence of contralateral renal parenhymal injury in patients with unilateral atherosclerotic renal artery stenosis. Ann. Vasc. Surg., 1998, 12, 122-127.

5. Guzman R.P., Zierler R.E., Isaacson J.A. et al. Renal atrophy and arterial stenosis. A prospective study with duplex ultrasound. Hypertension, 1994, 23, 346-350.

6. Zierler R.E., Bergelin R.O., Davidson R.C. et al. A prospective study of disease progression in patients with atherosclerotic renal artery stenosis. Am. J. Hypertens., 1996, 9,1055-61.

7. Caps M.T., Zierler R.E., Polissar N.L., et al. Risk of atrophy in kidneys with atherosclerotic renal artery stenosis. Kidney Int.,1998, 53, 735-742.

8. Rees C.R., Stent of atherosclerotic renovascular disease. J. Vasc. Int. Rad., 1999, 10, 689-705.

9. Gruntzig A., Kullmann U., Vetter W., Treatment of renovascular hypertension with percutaneous transluminal dilatation of a renal artery stenosis. Lancet, 1978, I, 801-802.

10. Klinge J., Mali W.P., Puijlaert C.B., et al. Percutaneous transluminal renal angioplasty: Initial and long-term results. Radiology, 1989, 171(2), 501-506.

11. Lossino F., Zuccalo A., Busato F., Zucchelli P. Renal artery angioplasty for renovascular hypertension and preservation of renal function: Long-term angiographic and clinical follow-up. Am. J. Roentgenol., 1994, 162(4), 853-857.

12. Bonelli F.S., Mckusick M.A., Tector S.C., et.al. Renal artery angioplasty: Technical results and clinical outcome in 320 patients. Mayo Clin. Proc., 1995, 70(11), 1041-52.

13. Jensen G., Zachrisson B.F., Dilin K., et al. Treatment of renovascular hypertension: One year results of renal angioplasty. Kidney Int., 1995, 48(6), 1936-45.

14. Henry M., Amor M., Henry I., et al. Stent placement in the renal artery. Three-year experience with the Palmaz stent. J. Vasc. Intervent. Radiol., 1996, 7(3), 343-350.

15. White C.J., Ramee S.R., Collins T.J., et al. Renal artery stent placement: Utility in lesions difficult to treat with balloon angioplasty. J. Am. Coll. Cardiol.,1997, 30(6), 1445-1450.
16. Harjai K., Khosla S., Shaw D., et al. Effect of gender on outcomes following renal artery stent placement for renovascular hypertension. Cathet .Cardiovasc. Diagn., 1997, 42(4), 381-6.
17. Harden P.N., MacLeod M.J., Rodger RSC. Effect of renal artery stenting on progression of renovascular mortality in hypertensive patients with renal artery stenosis. J. Hypertens., 1999, 17, 1743-50.
18. Safian R.D., Textor S.C. Medical Progress: Renal-Artery Stenosis. New Engl. J. Med., 2001, 6, 344.
19. Anderson W.P., Woods R.L. Intrarenal effects of angiotensin II in renal artery stenosis Kidney Int., 1987. 31 (Suppl. 20), 157-167.
20. De Cobelli F, Mellone R, Salvioni M, et al. Renal artery stenosis: Value of screening with three-dimensional phase-contrast MR angiography with a phased-array multicoil. Radiology, 1996, 201(3), 697-703.
21. Prince M.R., Schoenberg S.O., Ward J.S., et al. Hemodynamically significant atherosclerotic renal artery stenosis: MR angiographic features. Radiology, 1997, 205(1), 128-136.
22. Chen C.C., Hoffer P.B., Vahjen G. et al. Patients at high risk for renal artery stenosis: A simple method of renal scrintigraphic analysis with Tc-99m DTPA and captopril. Radiology, 1990, 176(2),365-370.
23. Schreij G., van Es P.N., van Kroonenburgh M.J. et al. Baseline and postcaptopril renal blood flow measurements in hypertensives suspected of renal artery stenosis. J. Nucl. Med , 1996, 37(10), 1652-1655.
24. Lerman L.O., Taler S.G., Textor S.C., et al: Computed tomography derived intrarenal blood flow in renovascular and essential hypertension. Kidney Int., 1996, 49(3), 846-854.
25. Schoenberg S.O., Knopp M.V., Bock M. et al: Renal artery stenosis: Grading of hemodynamic changes with cine phase-contrast MR blood flow measurement. Radiology, 1997, 203(1), 45-53.
26. Debatin J.E., Ting R.H., Wegmuller H. et al. Renal artery blood flow: Quantitation with phase-contrast MR imaging with and without breath holding. Radiology, 1994, 190(2), 371-378.
27. Ford K.K. et al. Percutaneous transluminal angioplasty vs. surgery for renovascular hypertension. Am. J. Roentgen., 1985, 144, 447-450.
28. Gardiner G.A., Stokes K.R. et al. Complications of transluminal angioplasty. Radiology, 1986, 159, 201-208.
29. Kidney D., Deutsch L.S. The indication and results of percutaneous transluminal angioplasty and stenting in renal artery stenosis. Semin. Vasc. Surg., 1996, 188-197.
30. Fournaud I., Denens C., Malex G., Nevelstin A. Renal artery angioplasty: current state of art. Angiologia i sosudistaya khirurgia, 2003, 9, 75-9.
31. Katzburg R.W. Urography into the 21st century: new contrast media, renal handling, imaging characteristics, and nephrotoxicity. Radiology, 1997,204,297-312.
32. Keizur J.J., Das S. Current perspectives on intravascular contrast agents for radiological imaging. J. Urol., 1994,151,1470-8.
33. Cohan R.H., Ellis J.H. Iodinated contrast material in uroradiology. Choice of agent and management of complications. Urol. North. Am., 1997,24,471-91.
34. Sovak M. Contrast media: a journey almost sentimental. Invest. Radiol., 1994, 29(Suppl 1), S4-S14.
35. Spring D.B., Quesenberry C.P. Jr. Costs of low-osmolar contrast media. JAMA, 1991, 266, 1081-2.
36. McClennan B.L. Preston M. Hickey memorial lecture. Ionic and nonionic iodinated contrast media: evolution and strategies for use. Am. J .Roentgenol., 1990,155,225-33.
37. Cohan R.H., Leder R.A., Ellis J.H. Treatment of adverse reactions to radiographic contrast media in adults. Radiol. Clin. North Am., 1996,34,1055-76.
38. Greenspan F.S. The thyroid gland. In: Greenspan F.S., Strewler G.J., editors. Basic and clinical endocrinology. 5th ed. Stamford, Conn., Appleton & Lange, 1997,192-262.
39. Plouin P.-F., Darne B., Chatellier G. et al. Restenosis after a first percutaneous transluminal renal angioplasty. Hypertension, 1993, 21, 89-96.
40. Lossino F., Zuccalo A., Busato F., Zucchelli P. Renal artery angioplasty for renovascular hypertension and preservation of renal function: Long-term angiographic and clinical follow-up. Am. J. Roentgenol ., 1994, 162(4), 853-857.
41. Jensen G., Zachrisson B.F., Dilin K., et al. Treatment of renovasular hypertension: One year results of renal angioplasty. Kidney Int., 1995, 48(6), 1936-45.
42. Plouin P.F., Chatellier G., Darne B., Raunaud A. Blood pressure out come of angioplasty in atherosclerotic artery stenosis: A randomized trial. Essai Multicentrique Medicaments vs Angioplastie (Emma) Study Group. Hypertension, 1998, 31(3), 823-9.
43. White C.J., Ramee S.R., Collins T.J., et al. Renal artery stent placement: Utility in lesions difficult to treat with balloon angioplasty. J. Am. Coll. Cardiol.,1997, 30(6), 1445-1450.

Subintimal Angioplasty for Multilevel Arterial Occlusion in a Patient with Chronic Critical Ischemia of Both Legs

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Introduction

Percutaneous transluminal angioplasty is a beneficial low-invasive method for treatment of patients with chronic critical ischemia, many of whom are elderly and have severe comorbidities. However, immediate and long-term results of standard intraluminal angioplasty have been unsatisfactory. A number of authors reported encouraging results of subintimal angioplasty in patients with chronic critical ischemia. This method was proposed as far back as 1989, however it is not widely known in Russia. We report our experience with successful subintimal angioplasty in a 79 year old female patient with multilevel arterial damage in both legs.

Clinical case

A female patient aged 79 with multiple comorbidities presented with multiple ulcers on the dorsum of both feet, ischemic pain at rest of over 4 weeks duration. Her ankle-brachial index was 0.15 and 0.19 on the right and left legs, respectively. Examination revealed bilateral occlusion of superficial femoral and popliteal arteries and proximal bilateral occlusion of all three crural arteries. Subintimal angioplasty of all involved vascular segments on both legs was performed. The patient shows stable clinical improvement 6 months following treatment. Her ankle-brachial index is 0.86 on the right and 0.84 on the left.

Discussion

Subintimal angioplasty was suggested over 10 years ago for treatment of extended chronic occlusions of superficial femoral artery and, later, for tibioperoneal and iliac arteries. The results of this intervention are close to those of bypass surgery. Relatively few papers have been published related to the use of this method. Even fewer authors report results which could be compared with those reported by the pioneers of this technique. Apparently, the method has some technical difficulties, and there are no universal views on patient selection and drug therapy accompanying the intervention.

Key words: critical leg ischemia, revascularization, subintimal angioplasty.

List of abbreviations:
chronic critical ischemia – CCI,
subintimal angioplasty – SA,
ankle-brachial index – ABI,
superficial femoral artery – SFA,
popliteal artery – PA.

Introduction Chronic critical ischemia (CCI) is a major indication for arterial bypass surgery in most vascular centres. According to Trans-Atlantic Inter-Society Consensus definition, revascularization in CCI aims at «ensuring blood flow sufficient to remove pain at rest and heal tissue defects. Ideal revascularization technique should require no general anesthesia, is associated with lower systemic stress and fewer complications" (9). Multilevel arterial occlusion and high incidence of extended occlusion is a rule rather than an exception in this category of patients. Traditional surgical approaches to revascularization are significantly restricted here, especially when the drainage vessels – crural arteries – are stenotic and occluded. Elderly age and severe comorbidities often make traditional surgical treatment impossible because of associated invasion and trauma.

Percutaneous endovascular interventions comply with many of the above requirements and are preferable. However, unsatisfactory immediate and long-term results of standard percutaneous transluminal angioplasty for vascular segments exceeding 5-10 cm give the ground for some skepticism (6, 7).

Several authors report encouraging results of intentional extraluminal recanalization, the so called subintimal angioplasty (SA) in patients with CCI. This method was proposed by A. Bolia in 1989 (1), however, due to some reasons it was not widely spread. Neither is this method well known in Russia, as seen from few related publications. We report our experience with successful SA in a 79 year old female patient with CCI and multilevel arterial occlusion in both legs.

Clinical case

A female patient aged 79 with multiple comorbidities presented with multiple ulcers on the dorsum of both feet, ischemic pain at rest of over 4 weeks duration. These symptoms, tissue defects and trophic lesions were more marked on the right leg. The patient reported history of intermittent claudication over many

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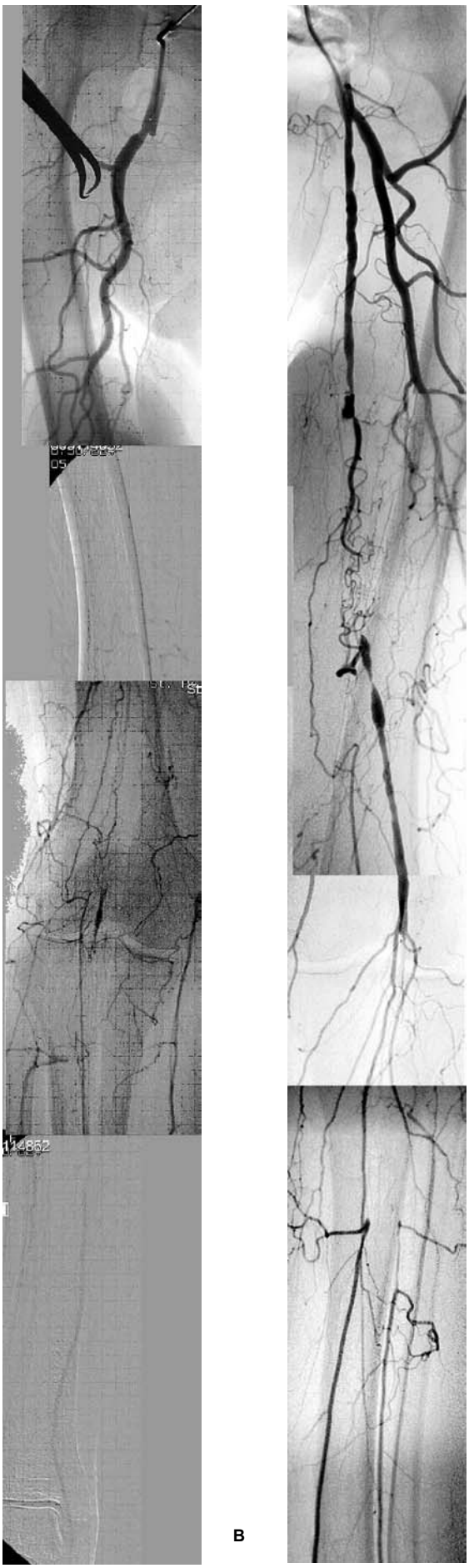

Figure. 1. Arteriograph of the left (A) and right (B) legs of patient P., 79 years old, with critical chronic ischemia.

years. Several years earlier the patient had suffered two myocardial infarctions and ischemic stroke, she also complained of arterial hypertension and permanent atrial fibrillation. The patient was also diagnosed with chronic bronchitis and pulmonary emphysema.

Her ankle-brachial index was 0.15 and 0.19 on the right and left legs respectively. Ultrasound duplex scanning of the leg arteries revealed bilateral occlusion of the superficial femoral (SFA) and popliteal arteries (PA) and proximal bilateral occlusion of all three crural arteries. Angiography through the left femoral access revealed the following: the right SFA was occluded along all its length, the right PA was contrasted in a short segment in its middle third, the right crural arteries were occluded proximally (Fig. 1A). The left SFA was occluded in its middle and distal thirds, PA was occluded downstream from the middle third, the left crural arteries were occluded proximally (Fig. 1B). Since conservative therapy proved inefficient, revascularization of the right leg by SA was performed immediately after diagnostic angiography. The patient received 0.5g Aspirin and 300mg Plavix orally. Following antegrade catheterization of the right common femoral artery, 5000IU of unfractioned heparin was injected through the 5F introducer. Intentional extraluminal recanalization of the occluded segment of SFA was performed using a 5F vertebral catheter and Glide 0.035 guidewire (Terumo, Japan) according to A. Bolia technique (3). Then a loop of the guidewire was formed again into in the short patent segment of PA and subintimal recanalization of occluded segment of the popliteal artery and anterior tibial artery was performed. Terumo guidewire was replaced with 0.018 SV-5 guidewire (Cordis, USA) and the recanalized segments of the anterior tibial and popliteal arteries were dilated using a 3x80 mm Savvy balloon (Cordis, USA) at 12 atm. Proximal PA and all SFA were dilated along the whole length using an Opta Pro 5x60 mm balloon catheter (Cordis, USA) at 12 atm. Follow-up angiogram showed antegrade blood flow in SFA, PA and anterior tibial artery. Short residual 50% stenosis was noted between proximal and middle thirds of PA. A 0.018 guidewire was left in the anterior tibial artery, and subintimal recanalization was performed again using a vertebral catheter and Terumo guidewire with subsequent angioplasty of the occluded tibioperoneal trunk and posterior tibial artery using a 3 mm balloon. Residual stenosis of the popliteal artery was eliminated by repeated dilation using a 5 mm balloon. Final arteriogram of the right leg is shown on Fig. 1A.

After the procedure the patient received Aspirin and Plavix according to the generally accepted protocol. The patient noted significant alleviation of pain in the right leg virtually immediately after the surgery. Soon crural edema disappeared. Over the subsequent two weeks granulation appeared and a tendency for ulcer healing was seen.

Three weeks after the above intervention subintimal recanalization and angioplasty of all occluded seg-

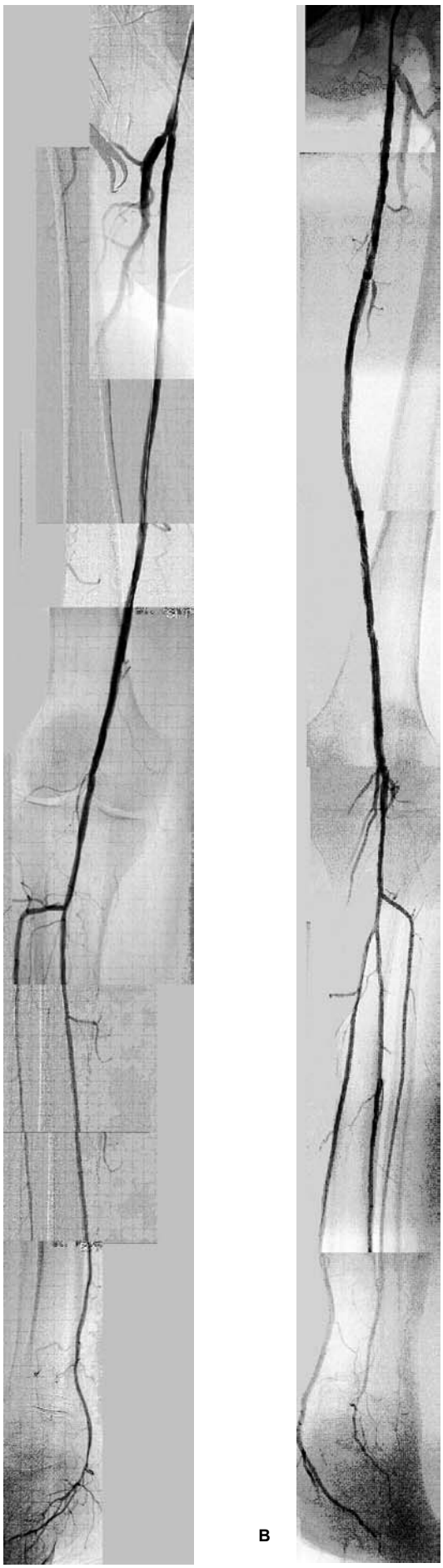

Figure 2. Arteriograph of the left (A) and right (B) legs of patient P., 79 years old, after subintimal angioplasty of the occluded arterial segments.

ments of SFA, PA and three crural arteries in the left leg was performed. Final angiogram is shown on Fig. 1B. Likewise, clinical improvement was noted on the left leg after correction of circulation. The patient shows stable clinical improvement 6 months following successful revascularization. Trophic lesions decreased markedly and the ulcers have almost healed. The pulsation can be palpated over the popliteal and crural arteries. The patient's ankle-brachial index is 0.86 on the right and 0.84 on the left.

Discussion

Significant progress has been obtained in CCI treatment over the last years due to achievements of endovascular techniques. Among these novelties is subintimal angioplasty, which was suggested over 10 years ago for treatment of extended chronic occlusions of superficial femoral artery and, later, for tibioperoneal and iliac arteries (1, 2). The first data on long-term results of this technique were published by Bolia et al. in 1994. The authors suggested this approach as an alternative to traditional bypass surgery (5). A retrospective comparison showed that long-term patency rate of recanalized vascular segments was inferior to that seen following bypass surgery; however, due to the simplicity of repeated interventions «secondary patency» following SA may come close to the results of surgical treatment. Moreover, in most cases reocclusion of vessels following SA did not cause recurrence of CCI nor threatened viability of the limb (4). Another feature of the described technique is the low percentage of need for stenting (less than 1% of surgeries) even following treatment of very long occlusions (5,8).

Despite the encouraging results, over 10 years, rather few papers focused on the use of this technique. Even fewer reported results are comparable to those reported by the pioneers of this technique (4). However, in these sparse centres angioplasty is the method of choice for treatment of patients with CCI and severe intermittent claudication. The small number of publications by no means indicates that this technique is not used by other vascular surgery centres. Likely, due to technical difficulties and disappointing initial results the surgeons stopped using the method without publishing their results. Apparently, a longer learning period is necessary, following which the results are improved. Lack of universal views on patient selection and drug therapy required by the intervention is an important contributing factor as well.

We started using the SA technique quite recently after thorough study of related publications. Our first experience is encouraging, and hereby we report an interesting case of successful complete revascularization in a patient with CCI due to multilevel occlusion of arteries in both legs using SA technique.

References:

1. Bolia A., Brennan J., Bell P.R. Recanalisation of femoro-popliteal occlusions: Improving success rate

by subintimal recanalisation. Clin. Radiol., 1989, 40,325.

2. Bolia A. Percutaneous intentional extraluminal (subintimal) recanalization of crural arteries. Eur. J. Radiol., 1998,28,199-204.

3. Bolia A., Bell P.R.F. Subintimal angioplasty. In: Dyet J.F., Ettles D.F., Nicholson A.A., Wilson S.E., editors. Textbook of endovascular procedures. 1st ed. Philadelphia, Churchill Livingstone, 2000, p. 126-38.

4. Desgranges P. et al. Subintimal angioplasty: feasible and durable. Eur. J. Vasc. Endovasc. Surg., 2004, 28,138-41.

5. Desgranges P. et al. Subintimal angioplasty of femoropopliteal artery occlusions: feasible and durable. Eur. J. Vasc. Endovasc. Surg., 1994, 28,138-155.

6. Matsi P.J., Manninen H.I., Suhonen M.T., Pirinen A.E., Soimakallio S. Chronic critical lower-limb ischemia: prospective trial of angioplasty with 1–36 months follow-up. Radiology, 1993, 188,381–387.

7. Desgranges P. et al. Prospective trial of infrapopliteal artery balloon angioplasty for critical limb ischemia:angiographic and clinical results. J. Vasc. Interv. Radiol., 2000, 11,1021–1031.

8. Spinosa D.J. Percutaneous Intentional Extraluminal Recanalization in Patients with Chronic Critical Limb Ischemia Radiology, Aug. 2004, 232, 499 - 507.

9. TASC TransAtlantic Inter-Society Consensus (TASC). Management of peripheral arterial disease (PAD). feasible and durable. Eur. J. Vasc. Endovasc. Surg., 2000, 19 (suppl.A), 208 - 290.

Contrast-Induced Nephropathy: A Primer for the Interventional Cardiologist

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Abstract

Contrast-induced nephropathy (CIN) is a foremost cause of in-hospital iatrogenic acute kidney failure. Post-procedural CIN is associated with a greater risk of requiring renal replacement therapy, prolonged hospitalization, undue health care costs, potential sustained decline in kidney function and death. Numerous risk factors for CIN have been identified and include pre-existing chronic kidney disease, diabetes mellitus, congestive heart failure, critical illness and volume of administered radiocontrast media. Interventions for the prevention of CIN remain controversial and uncertain.

This review will focus on current interventional evidence for the prevention of CIN. In general, several simple measures should be initially considered including correction of any underlying volume depletion, discontinuation of potential nephrotoxins, reversing any acute kidney dysfunction or when not possible, consideration to delay the interventional procedure or performing an alternative diagnostic test for imaging. In addition, an absolute minimum volume of radiocontrast media should be employed, including avoiding left venticulograms and performing staged interventions if applicable. There are few prophylactic interventions with quality evidence that demonstrate efficacy for prevention of CIN. Peri-interventional hydration and the use of non-ionic iso-osmolar radiocontrast media have consistently demonstrated efficacy. For patients with significant risk factors for CIN, there is evidence to suggest benefit with use of high dose N-acetylcysteine. Several clinical studies with adenosine antagonists such as theophylline, vitamin C and statins are hopeful; however, further confirmatory trials are needed. At present, there appears insufficient evidence for the routine use of hemodialysis or continuous hemofiltration, atrial natriuretic peptides, calcium channel blockers, or prostaglandins. The current evidence does not support the use of diuretic therapy, forced diuresis, low-dose dopamine, fenoldopam, captopril, or endothelin receptor antagonists.

While there have been advances in our understanding of the epidemiology, pathophysiology and natural history of CIN, few effective interventions have conclusively demonstrated evidence for a reduction in CIN and no therapy as yet has proven efficacious once CIN is established.

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INTRODUCTION

Acute renal failure (ARF) is common in hospitalized patients and is associated with an increased risk for death.(1-4) Despite advances in supportive medical therapy, the frequency of ARF continues to increase.(4) Iatrogenic factors are estimated to account for the majority of these episodes.(1, 5) Contrast-induced nephropathy (CIN) is the third most frequent cause of in-hospital ARF and the incidence will likely grow significantly with the broader utilization of radiocontrast media for diagnostic and interventional procedures.(4-6) CIN results in prolonged hospitalization, higher mortality rates, excessive health care costs and potentially long-term kidney impairment.(7-10) Moreover, CIN, or risk for CIN, may also delay or cancel important diagnostic or therapeutic procedures.

DEFINITION AND DIAGNOSIS

Numerous definitions for CIN appear in the literature; however, CIN has been generally defined as an acute decline in kidney function following the administration of radiocontrast media in the absence of other potential precipitants. While a diagnosis of CIN may appear obvious, other important determinants for the acute decline in kidney function, including atheroembolic disease, renal ischemia, and confounding nephrotoxins should be considered.(11-13) In research studies and for greater generalization of results and outcomes across clinical studies, CIN has traditionally been defined as an increase in serum creatinine of ≥25% or 44 mmol/L (0.5 mg/dL) above baseline.(5, 14) This change in serum creatinine has been correlated with both acute and long-term outcomes.(7, 15, 16)

Patients who develop CIN generally present with an acute rise in serum creatinine within 24 to 48 hours following injection of radiocontrast media. The ARF is usually non-oliguric and can be associated with an initial low fractional excretion of sodium.(17) Urine studies may reveal granular brown casts, tubular epithelial cells and mild proteinuria (<300 mg/day). An abnormal urinalysis or markers of renal tubular injury can be present despite no significant increase in serum creatinine.(18-20) Likewise, despite a clear increase in serum creatinine, the urinalysis can be bland and non-

diagnostic.(18) The serum creatinine level generally peaks within 3-5 days and returns towards baseline within 7-10 days; however, in some patients kidney function may not return to baseline and a persistent reduction in function may occur.(7, 15, 21, 22)

PATHOPHYSIOLOGY

Available experimental studies suggest that the pathophysiology of CIN is due to the interplay of direct tubular epithelial cell toxicity, alterations in renal hemodynamics with resultant ischemia, and concomitant atheroembolic showers of the renovasculature. While understanding the mechanisms contributing to the pathophysiology of CIN remains paramount for devising potential preventative strategies, this review will focus predominantly on the epidemiology, risk factors, outcomes and evidence for key interventions. More detailed reviews of the pathophysiology of CIN have been published.(23-25)

EPIDEMIOLOGY

Incidence: The incidence of CIN is highly variable due to differences in study populations and in the case-definition of CIN. Estimates of the incidence of CIN are also prone to selection bias due to the fact that the majority of data is derived from clinical trials or hospital-based studies representing in-patient populations. This becomes important to consider when the rate of diagnostic imaging or angiographic procedures being performed on an outpatient basis is increasing. To our knowledge, no population-based assessment of the epidemiology of CIN has been performed. However, CIN remains one of the most important, most common and predictable etiologies of ARF in hospitalized patients.(1, 2, 4) The range of reported incidence of CIN from hospital-based studies is 1-37%.(1, 7, 8, 15, 16, 18, 22, 26-28) In a prospective cohort study of 4,622 patients admitted to a tertiary care hospital, Nash et al. reported that CIN was the third most common etiology for hospital-acquired ARF occurring in an estimated 1% of subjects admitted to hospital, with the largest proportion of patients with CIN (49%) having undergone cardiac catheterization.(4) In two large retrospective studies of cardiac catheterization patients, 3.3-3.5% developed CIN, defined as an increase in serum creatinine ≥44 mmol/L(15) or ≥50% from baseline.(16) In a cohort study of 425 patients receiving adequate oral or intravenous hydration prior to percutaneous coronary interventions, only 1.4% of the subjects developed CIN.(28) However, when adjusting for pre-morbid chronic kidney disease, the incidence of CIN increases dramatically. In a prospective cohort study of 439 patients with known kidney disease (baseline serum creatinine ≥159 μmol/L) undergoing elective cardiac catheterization, 37% developed CIN (defined as increase in serum creatinine ≥25% or need for RRT within 48 hours of the procedure).(7)

Risk Factors: Transient declines in kidney function after radiocontrast media administration have been reported in almost all patients (29, 30); however, clinically important reductions in kidney function are exceedingly uncommon in patients with normal baseline kidney function.(5, 14) Clinically important declines in function are generally associated with the presence of pre-existing risk factors. (Table 1) Rich et al. demonstrated in patients undergoing cardiac catheterization that the incidence of CIN increased from 1.2 to 100% when the quantity of risk factors increased from none to four.(31) Likewise, Rihal et al.demonstrated that the risk of CIN was higher in diabetics compared with non-diabetics among those with baseline serum creatinine <177 mmol/L and higher for all patients with a baseline serum creatinine ≥177 mmol/L.(15)

Table 1. Risk Factors for development of contrast-induced nephropathy.

Established Risk Factors
Pre-existing chronic kidney disease
High dose (volume) of radiocontrast media
Presence of diabetes mellitus
Age > 70 years
Acute myocardial infarction
Decreased effective arterial volume
Mean arterial pressure < 100 mmHg
Use of intra-aortic balloon pump
Shock
Congestive heart failure
Cirrhosis
Nephrotic syndrome
Repeat radiocontrast media within 48 hours
Putative Risk Factors:
History of atopy
Hypertension
Multiple myeloma
Use of selective or non-selective non-steroidal anti-inflammatory drugs
Use of ACE inhibitors or angiotensin receptor blockers
Use of diuretics
Low ejection fraction (<50%)
Intra-procedural events
Complex percutaneous coronary interventions
Intra-arterial radiocontrast media injection

In several epidemiologic studies, multivariate analyses have suggested that the presence of pre-existing chronic kidney disease [glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2], a diagnosis of diabetes mellitus, quantity of radiocontrast media administered, the presence of hypertension or hypotension, increased age, anemia, recent acute myocardial infarction, history of congestive heart failure, use of an intra-aortic balloon pump, and the presence of shock are independently associated with a risk for development of CIN.(15, 21, 27, 31-39)

A variety of other risk factors have been reported and include a history of atopy, concurrent nephrotoxic medications (e.g. non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors), use of furosemide, concomitant states of decreased effective circulating blood volume (e.g. congestive heart failure, liver cirrhosis, nephrotic syndrome), low ejection fraction (<50%), and intra-arterial administration of radiocontrast media.(7, 31, 35, 37, 40-45) Multiple myeloma has been suggested as a risk factor but no prospective or randomized data at present exists. The available studies are limited due to retrospective design and failure to control for differences in volume

depletion, hypercalcemia, severity of proteinuria, infection or the utilization of potentially nephrotoxic antibiotics.(46, 47) Overall, several studies support the concept that the most important risk factors for the development of CIN are the presence of pre-existing chronic kidney disease or diabetes mellitus.(15, 21, 27, 30-32, 38, 39, 48)

Mehran et al. have prospectively developed and validated a simple scoring scheme for the risk stratification for CIN, defined as an increase of ≥25% or ≥44μmol/L in serum creatinine from baseline, and need for in-hospital RRT for patients undergoing cardiac catheterization or percutaneous coronary intervention (Table 2).(39) This scoring assessment is derived from clinical information that is generally widely available and could be easily incorporated for both patients and clinicians at the bedside.

Incident renal replacement therapy and mortality: Contrast-induced nephropathy complicated by need for RRT is infrequent occurring in approximately 0.4-1.1% of patients; however, higher rates have been reported and again are primarily dependent on the population being assessed.(4, 7, 8, 18, 27, 49)

Table 2. Prediction of risk for development of contrast-induced nephropathy for patients referred for cardiac catheterization or percutaneous coronary intervention (Modified from reference(39)).

Risk Factor	Integer Score
Hypotension	5
Use of intra-aortic balloon pump	5
Congestive heart failure	5
Age 75 years	4
Anemia	3
Diabetes mellitus	3
Volume of radiocontrast media	1 per 100 mL
Serum creatinine 133 μmol/L OR GFR < 60 mL/min/1.73 m^2: 40-60 mL/min/1.73 m^2 20-40 mL/min/1.73 m^2 < 20 mL/min/1.73 m^2	 4 OR 2 4 6

Risk Score	Risk of CIN (%)	Risk for in-hospital RRT (%)
≤ 5	7,5	0,04
6-10	14,0	0,12
11-15	25,1	1,1
≥ 16	57,3	12,6

Abbreviations: IABP = intra-aortic balloon pump; GFR = glomerular filtration rate; CIN = contrast-induced nephropathy; RRT = renal replacement therapy.

Definitions: hypotension = systolic blood pressure <80 mmHgfor at least 1 hour requiring inotropic support or IABP within 24 hours of procedure; congestive heart failure = class III/IV or prior pulmonary edema; anemia = baseline hematocrit <39% for mean and <36% for women.

In a cohort study of 1,826 consecutive patients referred for cardiac catheterization, McCullough et al. reported that 14.5% patients developed clinically important declines in kidney function attributed to radiocontrast media exposure with 0.5% requiring incident RRT.(27) Risk factors independently associated with need for RRT included reduced baseline creatinine clearance (CrCl), presence of diabetes mellitus and increased radiocontrast media dose. Of note, no patient receiving <100 mL radiocontrast media or with a baseline CrCl ≥47mL/min required acute RRT.

In a prospective study of diabetic patients with moderate to severe chronic kidney disease (mean baseline creatinine 522 μmol/L) referred for cardiac catheterization, CIN occurred in 50%, with 15% of patients ultimately requiring RRT within 14 days.(37) Similarly, in a prospective cohort of 439 chronic kidney disease patients (serum creatinine ≥159 μmol/L) referred for cardiac catheterization, Gruberg et al. reported that 19% developed CIN and 7% overall required acute RRT, with 4 patients failing to become independent of RRT by hospital discharge.(7)

Independent factors associated with CIN requiring RRT included increasing age, hypertension, diabetes mellitus, prior coronary artery bypass surgery, chronic kidney disease and a reduced left ventricular ejection fraction.(49) Furthermore, the need for RRT resulted in greater morbidity and utilization of health care resources with higher rates of post-procedural myocardial infarction, vascular and bleeding complications and prolonged duration of hospitalization.(49)

In general, the outcomes associated with CIN have been most often evaluated in patients referred for cardiac catheterization. In this population, CIN is associated with a reduction in both short and long-term survival. Several epidemiologic studies have reported hospital and 1-year mortality rates in the range of 15-34% and 35-36%, respectively.(7, 8, 15, 38) In one study, long-term mortality rates in patients with CIN, conditional on hospital discharge, were 9.8%, 12.1% and 44.6% at 6-months, 1-year and 5-years, respectively.(15) For those who require initiation of RRT, the prognosis is worse and the mortality rates are considerably higher with estimated hospital, 1-year and 2-year mortality rates of 12-39%, 45-55% and 81%, respectively.(7, 8, 15, 27, 49, 50)

INTERVENTIONS FOR THE PREVENTION OF CIN

CIN is potentially preventable considering that the administration of radiocontrast media is often associated with a planned procedure. Considerable efforts have been undertaken to prevent or minimize the risk of this complication. However, the clinical impact of tested interventions has often been limited by conflicting results, inadequately powered trials, and inconsistency in the primary outcome definition.(51, 52) The following is a critical appraisal of the available evidence for kidney protection and the prevention of CIN.(Table 3)

Interventions with Evidence of Benefit

Peri-procedural Hydration - In patients with chronic kidney disease, the administration of intravenous fluids in isolation has not been shown to completely ameliorate CIN; however, intravenous fluids have long been recognized as a means to reduce the likelihood

Table 3. Summary of clinical trial evidence for the prevention of contrast-induced nephropathy.

Beneficial
Hydration and/or Volume repletion
Iso-osmolar non-ionic radiocontrast media
Conflicting or Unclear Evidence
N-acetylcysteine
Ascorbic Acid (Vitamin C)
Statins
Adenosine antagonists
Prophylactic RRT
Prostaglandins
Calcium channel blockers
No Effect or Potential Harm
Forced diuresis
Low-dose dopamine
Fenoldopam
Atrial natriuretic peptide
Endothelin receptor antagonists
Captopril

Abbreviations: RRT = renal replacement therapy

of CIN for patients with clinical risk factors.(26, 53-55) Indirect evidence supporting hydration for the prevention of CIN derives from randomized studies where a hydration protocol in the control group was used in comparison to hydration with other interventions such as forced diuresis; however, considering the absence of a non-hydration control group, the results may falsely imply a direct benefit to hydration alone.(10, 26, 45, 55) Nevertheless, several clinical studies have emerged assessing a variety of protocols for peri-procedure hydration. (Table 4)

In an attempt to reduce overnight hospitalization for outpatient cardiac catheterization procedures, an aggressive oral hydration protocol was compared to standard intravenous hydration for 36 chronic kidney disease patients (baseline serum creatinine ?124µmol/L) referred for elective cardiac catheterization.(56) The investigators found no significant difference in the maximal change in serum creatinine at 48 hours or in the incidence of CIN. In contrast, a prospective randomized study reported an intravenous isotonic hydration protocol was superior to unrestricted oral fluids for reduction the incidence of CIN (3.7% vs. 34.6%, p=0.005) in 53 patients undergoing elective cardiac catheterization.(57) Likewise, Bader and colleagues suggested that intravenous hydration was superior to oral hydration in patients with normal baseline kidney function.(58) The discrepancy between these trials may be accounted for by fundamental differences in methodology, specifically the hydration protocols. The oral hydration group in the study by Taylor et al. had a prescribed volume of 1000 mL of water to be taken in the 10 hours preceding cardiac catheterization followed by a six-hour intravenous 0.45% normal saline infusion at 300 mL/hr initiated prior to radiocontrast media exposure. Therefore, patients in the oral hydration group received on average 1000mL more volume, whereas patients in the oral hydration group in the study by Trivedi et al. were simply allowed unrestricted oral fluids with no minimum requirements.

A recent prospective, randomized controlled open-label study of patients referred for cardiac catheterization compared isotonic hydration (0.9% saline) with hypotonic hydration (0.45% saline) for the prevention of CIN.(59) Although patients were mostly non-diabetic and had near normal baseline kidney function (mean baseline CrCl 84 mL/min), hydration with isotonic saline was associated with a 1.3% absolute risk reduction in the incidence of CIN (p=0.04). On subgroup analysis, those with diabetes mellitus and those administered ≥250 mL radiocontrast media had the greater benefit from isotonic saline hydration.

Recently, sodium bicarbonate has been hypothesized to reduce the incidence of CIN by acting as a buffer of free radicals generated in renal tubules following the administration of hyperosmolar radiocontrast media. In a single-center randomized trial of 119 patients undergoing elective diagnostic imaging, Merten et al. report an 11.9% absolute risk reduction in CIN, defined as a 25% increase in serum creatinine at 48 hours, for sodium bicarbonate (sodium 154 mEq/L) compared with normal saline (sodium 154 mEq/L) hydration (1.7% vs. 13.6%; p=0.02). (60) Despite several limitations, including a small, single-center study, unscheduled early termination of the study and loss-to follow-up of 18 patients, the results

Table 4. Summary of clinical trials of hydration for prevention of contrast-induced nephropathy.

Trial	Study Design	N	Baseline Kidney Function	Hydration Protocol	Incidence of CIN	Conclusion
Eisenberg (54)	Prospective cohort	537	N/A	Non-specific hydration	No CIN	Reduced risk with hydration
Taylor (56)	RCT	36	SCr > 124 µmol/L	PO + IV vs. IV	No CIN	PO and IV equivalent
Trivedi (57)	RCT	53	SCr > 106 µmol/L	PO vs. IV	PO 34.6% vs. IV 3.7%	IV superior
Mueller (59)	RCT	1383	GFR < 84 mL/min	0.9%NS vs. 0.45%NS	0.9%NS 0.7% vs. 0.45%NS 2.0	0.9%NS superior
Bader (58)	RCT	63	GFR < 107 mL/min	PO vs. IV vs. PO + IV	IV 28% vs. PO 48% vs. PO + IV 55%	IV superior to PO plus IV or PO alone
Merten (60)	RCT	119	SCr > 97 µmol/L	$NaHCO_3$ vs.0.9%NS	$NaHCO_3$ 1.7%vs. 0.9%NS 13.6%	$NaHCO_3$ superior

Abbreviations: N/A: not available; SCr: serum creatinine; CIN: contrast-induced nephropathy; RCT: randomized controlled trial; ARR: absolute risk reduction; GFR: glomerular filtration rate; NaHCO3 = sodium bicarbonate

of this seemingly simple intervention are promising.

The cumulative literature would suggest that volume depletion be avoided in patients with a planned procedure in which radiocontrast media will be administered. Furthermore, there is reasonable evidence for active peri-procedure hydration for those patients who can tolerate volume loading, either with isotonic saline or isotonic bicarbonate for prevention on CIN.

Type of Radiocontrast media - There has been considerable controversy as to whether the type of radiocontrast media administered (e.g. ionic vs. non-ionic, iso- osmolarity vs. low- osmolarity vs. high osmolarity) can reduce the frequency of CIN. In patients with normal kidney function, there is no significant benefit of using non-ionic compared with ionic agents.(61, 62) However, a randomized, double-blind multicenter trial of 1196 patients demonstrated a benefit of non-ionic (iohexol) vs. ionic radiocontrast media in subjects with chronic kidney disease and diabetes mellitus.(21) A meta-analysis of all randomized trials prior to 1991 comparing high and low-osmolarity radiocontrast media suggested a reduction in CIN with low-osmolarity radiocontrast media for patients with chronic kidney disease.(61) Recently, a multicenter, randomized, double-blind, study compared the effects of iso-osmolar non-ionic (iodixanol) vs. low-osmolar non-ionic (iohexol) radiocontrast media in 129 high-risk patients (pre-existing chronic kidney disease and diabetes mellitus) referred for cardiac catheterization or aortofemoral angiography.(63) The primary outcome was peak change in serum creatinine from baseline to 72 hours following administration of radiocontrast media. The use of iso-osmolar contrast (iodixanol) resulted in a significantly lower peak increase in serum creatinine compared with the low-osmolar radiocontrast (iohexol) and a 23% absolute risk reduction in CIN (3% vs. 26%, p=0.002). The cumulative data available at present would suggest evidence for the preferential use of non-ionic iso-osmolar (e.g. iodixanol) radiocontrast media in patients at risk for CIN along with an attempt to administer the minimum total volume of radiocontrast media required to safely and adequately perform the procedure.

Interventions with Inconclusive Evidence

Anti-oxidants - N-acetylcysteine (NAC) is a thiol containing antioxidant with applications in various clinical conditions, most commonly as prophylaxis for fulminant hepatic failure as a result of acetaminophen toxicity.(64) The activity of NAC is believed mediated through its properties as a scavenger of free-radical species and increasing the synthesis of nitric oxide, a potent vasodilator, in response to ischemic or other toxic injury in the kidney.(65-67) Tepel et al. was first to demonstrate in a small randomized controlled trial of 83 patients with stable chronic kidney disease (mean baseline creatinine 221 μmol/L) referred for elective computerized tomography scans requiring intravenous radiocontrast media (all received 75 mL) that NAC plus hydration compared with hydration alone resulted in a reduction in the incidence of CIN (2% vs. 21%; P=0.01).(68) Thereafter, numerous studies have been published addressing the efficacy of NAC for prevention of CIN with highly variable and conflicting results.(69-90)

Interestingly, in two studies where NAC was found effective, the subjects randomized to placebo had no significant mean increase in serum creatinine as expected for those at risk for CIN following radiocontrast media administration.(68, 77) In contrast, those subjects assigned to NAC experienced a mean decrease in serum creatinine and improvement in creatinine clearance after radiocontrast media exposure. The improvement in kidney function with NAC is unexplained.(91) Kay et al. suggest that the vasodilatory properties of NAC may have contributed to improvements in renal hemodynamics and partly explain the reduction in serum creatinine and increase in creatinine clearance in patients receiving NAC.(77) Others have hypothesized that NAC interferes with assays for serum creatinine, that NAC increases renal tubular clearance of creatinine or reduces endogenous production of creatinine.(52, 92) Estimates of creatinine clearance that utilize a prediction formula based on serum creatinine or 24 hour urinary collections of serum creatinine may still overestimate the improvement in kidney function if any of the above hypotheses are correct. No studies have reported the effect of NAC on more direct measures of glomerular filtration such as clearance of iothalamate, inulin or cystatin C.

Numerous systematic reviews have aimed to clarify whether NAC is efficacious for prevention of CIN.(93-100) Several of the meta-analyses that suggest an overall risk reduction with use of NAC did not adequately account for the heterogeneity among trials nor the suggestion of publications bias.(93, 94, 99) A more recent meta-analysis, including a greater number of randomized controlled trials, reported that NAC may be protective - the pooled relative risk for CIN was 0.65 (95% CI 0.43-1.0, p=0.05).(98) However, the considerable heterogeneity across trials remained unexplained.(98, 100, 101) An updated summary of published randomized controlled trials of NAC enrolling a total of >2,500 patients referred for cardiac catheterization is displayed in Figure 1.

One hypothesis that has emerged from the available literature on NAC is that the kidney protective effects may be dependent on the total dose of NAC, route of administration, and baseline kidney function.(70, 72, 74, 87, 89) In general, clinical trials that have used a high total dosage of NAC (>4,000 mg) have been associated with significant reductions in CIN.(72, 74, 80, 87, 89) The Rapid Protocol for the Prevention of Contrast-induced Renal Dysfunction (RAPPID) trial compared high-dose intravenous NAC (150 mg/kg in 500 mL 0.9%NS over 30 min before the procedure and 50 mg/kg in 500 mL 0.9%NS after the procedure) to hydration alone in 80 chronic kidney dis-

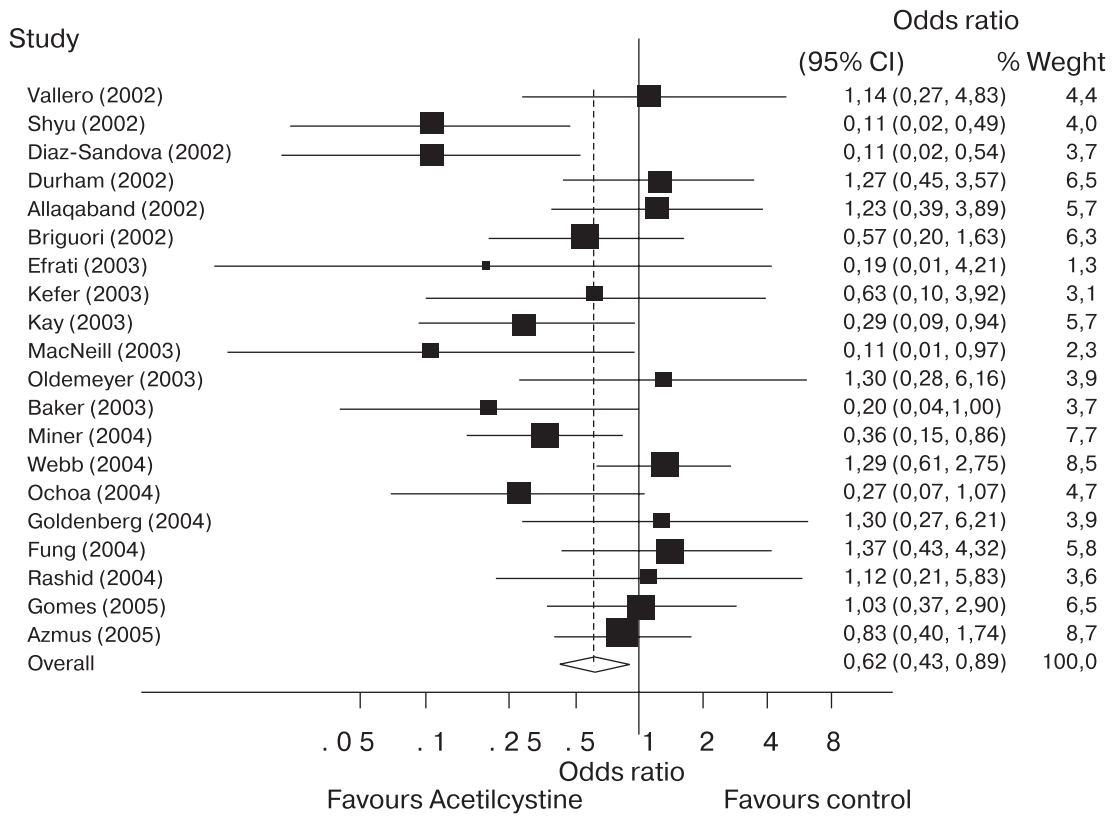

Figure 1. Forest plot of weighted odds ratios for contrast-induced nephropathy from 20 randomized clinical trials that use N-acetylcysteine in patients undergoing cardiac catheterization.[Test for heterogeneity (Q) =32.2, p=0.03; I2 = 41.0%].

ease patients (mean baseline serum creatinine 160 µmol/L) referred for cardiac catheterization.(70) Both groups received similar volumes of non-ionic iso-osmolar (iodixanol) radiocontrast media. Based on an average patient weight of 80 kg, the cumulative dose of NAC administered in this study was approximately 16,000 mg. This is considerably larger quantity of NAC than given in any other clinical trial to date. The higher dose protocol resulted in a significant reduction in CIN when compared with hydration alone (5% vs. 21%, p=0.05). Similarly, in a randomized trial of 224 chronic kidney disease patients referred for cardiac catheterization, Briguori et al. demonstrated a reduced incidence of CIN with a double-dose NAC protocol (1,200mg PO twice daily) compared with a standard dose NAC (600 mg PO twice daily) regimen (3.5% vs. 11%, p=0.04).(72) In this study, the procedures were elective, permitting adequate hydration and all patients received non-ionic, low-osmolality radiocontrast media. These investigators have further compared low-osmolarity (iobitridol) and iso-osmolarity (iodixanol) radiocontrast media in 225 chronic kidney disease patients (baseline serum creatinine ≥133 µmol/L) all receiving prophylaxis with double-dose NAC (1200 mg PO twice daily).(102) There was no significant difference in the incidence of CIN between low-osmolarity or iso-osmolarity radiocontrast media (2.7% vs. 3.5%, p=0.6). Finally, while the use of NAC is associated with a reduction in CIN, there is no evidence at present that NAC improves either short or long-term outcomes.(87)

Although encouraging, results across studies have been variable and difficult to interpret with certainty. Taken together, the results of these studies should be viewed as promising evidence of benefit, and suggest that it is reasonable to use NAC in routine care because of its relative ease of use, low cost, and favourable safety profile. Ideally a well-designed multicentre trial is required that incorporates clinically meaningful endpoints, rather than intermediate endpoints based on changes in serum creatinine.(51, 52, 103)

Given its anti-oxidant properties, ascorbic acid has also been tested for the prevention of CIN. A recent randomized trial of 231 patients with mild chronic kidney disease (mean baseline serum creatinine 106 µmol/L) referred for cardiac catheterization reported a reduced incidence of CIN in those receiving ascorbic acid (5 gm) peri-procedure compared with placebo. The occurrence of CIN was 9% in the ascorbic acid group and 20% in those randomized to placebo (p=0.02).(104) While provocative, confirmatory studies are required. Further, a concern regarding potential oxalate supersaturation also exists with the use of high dose ascorbic acid.(105)

Haeussler et al. reported the presence of increased reactive oxygen species after in vitro exposure of cultured human proximal renal tubular cells exposed to hydrogen peroxide that was attenuated by the concomitant administration of the antioxidant sodium-2-mercaptoethane sulphonate (MESNA).(106) These authors further tested this antioxidant in 12 patients with stable chronic kidney disease (mean baseline serum creatinine 296 µmol/L) prior to cardiac

Table 5. Summary of clinical trials of adenosine antagonists for prevention of contrast-induced nephropathy.

Study Author	Study Design	N	Baseline Kidney Function	Adenosine Antagonist Protocol	Incidence of CIN	Conclusion
Gandhi (116)	NR	21	NR	TH 125 mg PO bid 24 hr pre and 48 hr post	TH 15% vs.control 13%	No benefit
Erley (117)	RDBPCT	39	GFR 75-78 mL/min	TH 5 mg/kg IV 45 min prior	GFR stable with TH	TH superior
Katholi (29)	RCT	93	GFR 79-82 mL/min	TH 2.88 mg/kg PO q12 hr x 4 doses starting 1 hr prior	GFR reduced less with TH & non-ionic contrast	TH superior
Kolonko (122)	RBDPCT	58	GFR 106-108 mL/min	TH 165 mg IV 30 min prior	GFR stable with TH	TH superior
Abizaid (10)	RCT	40	SCr 168-203 mol/L	TH 4mg/kg bolus then 0.4 mg/kg/hr infusion	TH 35% vs. PL 30%	No benefit
Erley (118)	RDBPCT	80	SCr 150-168 mol/L	TH 270mg PO qam, 540 mg PO qpm 24 hr pre and 72 hr post	TH 5.7% vs. PL 3.4%	No benefit
Kapoor (119)	RCT	70	SCr 102-106 mol/L	TH 200 mg PO bid 24 hr pre, 48 hr post	TH 3% vs. Control 31%	TH superior, use of high-osmolar radio-contrast media
Huber (42)	RDBPCT	100	SCr 170-183 mol/L	TH 200 mg IV 30 min prior	TH 4% vs. PL 20%	TH superior

Abbreviations: NR = not recorded or available; RBDPCT = randomized double blind placebo controlled trial; RCT = randomized controlled trial; TH = theophylline or aminophylline; PL = placebo; GFR = glomerular filtration rate; SCr = serum creatinine.

catheterization by intravenous administration of MESNA 800mg along with normal saline hydration. The results demonstrated a reduction in reactive oxidant activity and no significant difference change in serum creatinine assessed at 48 hours.(106)

Experimental studies have suggested that hydroxymethoylglutaryl coenzyme A (statin) therapy, perhaps via pleiotropic effects on the vasculature, can reduce expression of reactive oxygen species following exposure to radiocontrast media.(107) Recently, statin therapy has been hypothesized and proposed to protect against CIN in patients undergoing cardiac catheterization.(108, 109) In a large study of a cardiac catheterization registry, Khanal et al. suggested that pre-procedure therapy with statins reduced not only the incidence of CIN (4.4% vs. 5.9%, p<0.001) but also incident RRT (0.32% vs. 0.49%, p=0.03).(109) However, there are several methodological concerns with this study that limit the apparent inference of benefit with statin therapy in addition to the marginal absolute clinical differences noted. Specifically, there were significant differences in the baseline characteristics of those designated as statin vs. no statin therapy, not all important confounders for the observed increase in serum creatinine were accounted for, and concerns regarding the use of propensity score adjustment in regression modelling in the context of a low event rate.(110) While there results are provocative and encouraging, further confirmatory studies are needed.

Adenosine receptor antagonists - Elevated endogenous adenosine may contribute to the pathophysiology of acute reductions in kidney function following radiocontrast media exposure.(111, 112) Increased urinary excretion of adenosine has been demonstrated following the intravascular administration of radiocontrast media.(113) In experimental models, adenosine-receptor antagonists attenuate the vasoconstrictive effects observed with radiocontrast media and preserve both renal blood flow (RBF) and glomerular filtration perfusion pressure.(114, 115) Small clinical trials in patients with chronic kidney disease suggest that the prophylactic use of theophylline, an adenosine-receptor antagonist, may prevent or ameliorate the expected decline in kidney function; however, results are inconsistent across trials.(10, 29, 42, 116-122) (Table 5) In two of these trials, high-osmolality ionic radiocontrast media was used and baseline kidney function was only marginally reduced.(29, 117, 122) Another small cohort study demonstrated no benefit for prophylactic intravenous aminophylline in prevention of CIN for patients referred for angiography.(121) Likewise, Erley et al. reported no significant preservation in kidney function in a randomized controlled trial of 80 chronic kidney disease patients (mean baseline serum creatinine 150 μmol/L) comparing prophylactic theophylline plus hydration to hydration alone.(123) These results were similar to a trial where prophylactic aminophylline failed to reduce the incidence of CIN when compared to hydration alone.(10) In contrast, Kapoor et al. reported that prophylactic theophylline resulted in a risk reduction for development of CIN after high-osmolar ionic radiocontrast media exposure in 70 diabetic patients (mean baseline serum creatinine 102 μmol/L) referred for cardiac catheterization.(119) Huber et al. reported results of a randomized controlled trial of intravenous

theophylline prophylaxis in 100 patients (mean baseline serum creatinine 115 µmol/L) receiving a minimum 100 mL of low-osmolality radiocontrast media.(42) An increase in serum creatinine >44 mmol/L was the primary endpoint. Theophylline resulted in a reduced risk of CIN compared with placebo (4 % vs. 16 %, p=0.05). Although these results are provocative, the trial is limited by baseline differences between the patients assigned the two interventions and the clinical relevance of the primary outcome.

Two recent systematic reviews have independently concluded that adenosine antagonists may reduce the incidence of CIN.(124, 125) The pooled odds ratio for CIN with theophylline demonstrated a trend towards significance at 0.40 (95% confidence interval, 0.2-1.2, p=0.09).(125) (Figure 2) Overall, these results are encouraging and adenosine antagonists may have a role in prevention of CIN; however, due to the borderline significance and variable findings reported across trials, there is a need for a confirmatory large well-designed trial.(124, 125)

Prophylactic renal replacement therapy - Hemodialysis can effectively remove radiocontrast media from the circulation following administration.(126-131) Preventative RRT has been proposed for high-risk patients following angiography with the rationale that removing radiocontrast media from the circulation ameliorates nephrotoxicity.(Table 6) Lehnert et al. randomized 30 chronic kidney disease (mean baseline serum creatinine 212µmol/L) patients to 3 hours of RRT or no RRT immediately following the administration of radiocontrast media, with no significant difference in the occurrence of CIN between the groups.(131) Likewise, similar trials of RRT for removal of radiocontrast media have failed to demonstrate significant reductions in CIN.(127-130, 132, 133) Furthermore, recent evidence suggests that prophylactic RRT may be associated with an increased risk of complications.(134) The ischemic and toxic damage induced by radiocontrast media are in part, likely immediate; therefore, efforts at removal following intravenous administration are not indicated nor of proven benefit in the absence of complications from ARF.(135)

A recent randomized trial compared continuous veno-venous hemofiltration (CVVH) (neutral balance with QB 100 mL/min and replacement isotonic saline 1000 mL/hour) to isotonic saline hydration alone (1 mL/kg/hour) in 114 high-risk patients with chronic kidney disease (baseline serum creatinine >177 µmol/L) referred for elective cardiac catheterization.(136, 137) The primary outcome was CIN defined as 25% increase in serum creatinine from baseline. Continuous hemofiltration was associated with a significant reduction in CIN compared with isotonic hydration (5% vs. 50%, p<0.001). Also, the investigators demonstrated that receiving CVVH resulted in reduced in-hospital (2% vs. 10%, p=0.02) and 12-month (10% vs. 30%, p=0.01) mortality. However, the results of this trial should be interpreted with caution due to several concerning features. First, the investigators instituted CVVH for oliguria >48 hours or the

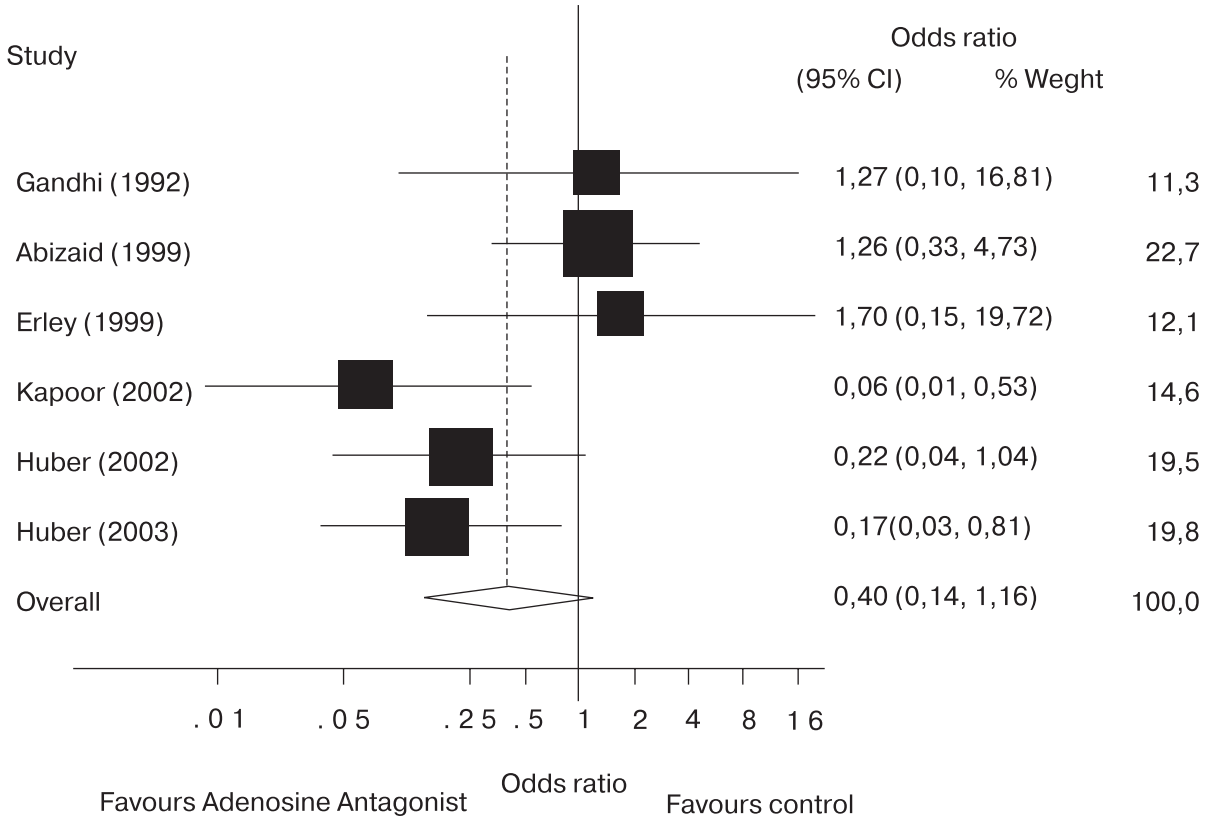

Figure 2. Forest plot of weighted odds ratios for contrast-induced nephropathy from six randomized clinical trials that use adenosine antagonists [Test for heterogeneity (Q) =9.8, p=0.08; I2 = 48.8%] (Modified from reference (125)).

development of pulmonary edema. This resulted in 25% of control patients initiating RRT during the study period – an unexpectedly high incidence. Second, defining CIN by absolute changes in serum creatinine may bias towards a lower incidence of CIN in patients receiving CVVH due to increased clearance of creatinine by CVVH. Furthermore, the results are potentially confounded by CVVH patients having received monitoring in intensive environment with greater attention to intravascular volume status. This group has now reported a similar trial of variable protocols of continuous hemofiltration for prevention of CIN.(138) However, in general, due to the numerous methodological concerns, the complexity of the intervention, the cost of providing CVVH and intensive care unit admission, this therapy should not be routinely performed outside of the usual indication for providing RRT in ARF or in circulatory overload in patients with congestive heart failure.(139)

Prostaglandins - Prostaglandin E1 (PGE1) is a vascular endothelial peptide that can induce vasodilation and counteract the vasoconstrictive actions of ischemic or toxic injury in the renal circulation.(140, 141) Chronic kidney disease may alter and reduce the local production of prostaglandins prompting unopposed and sustained vasoconstriction upon exposure to radiocontrast media.(142) A randomized controlled study of 130 patients with chronic kidney disease (mean baseline serum creatinine 159 μmol/L) that compared three doses of PGE1 infusions (10 ng, 20 ng and 40 ng) with placebo found a smaller increase in serum creatinine in patients receiving 20ng dose of PGE1 following radiocontrast media exposure.(143, 144) Unfortunately, the groups were not balanced at baseline and no clinically relevant differences in outcomes were found. The authors went on to hypothesize that a low-dose PGE1 infusion may prevent CIN; however, PGE1 should not be routinely prescribed until further corroborating trials are completed.

Calcium channel blockers - Calcium channel blockers (CCB), perhaps by inducing renal vasodilation, have been shown in animal models to prevent reductions in RBF induced by radiocontrast media.(114, 145, 146) However, evidence from clinical studies remains inconclusive.(147, 148) Two small randomized controlled trials suggest that a prophylactic dose of a CCB ameliorates the decline in GFR following administration of radiocontrast media.(149, 150) On the contrary, two other randomized trials failed to show evidence of any differences in excretion of urinary markers of renal injury, kidney function or incidence of CIN following a single prophylactic dose of a CCB.(20, 151) In one clinical trial that randomized 111 patients with near-normal kidney function to receive single dose nifedipine plus hydration prior to radiocontrast media or hydration alone.(152) Only 85 patients were included in the analysis and there were significant differences in baseline characteristics of the groups. Overall, there was no clinically relevant difference in kidney function with the addition of nifedipine. Based on the available data, there is inadequate evidence to support the use of CCB for prevention of CIN. Results of a larger randomized trial will hopefully determine whether CCB can prevent or ameliorate radiocontrast

Table 6. Summary of clinical studies of prophylactic renal replacement therapy for prevention of contrast-induced nephropathy.

Trial	Study Design	N	Baseline Kidney Function	Intervention	Outcomes	Conclusions
Lehnert(131)	RCT	30	SCr 200-228 mol/L	Single session post-IHD vs. Control	CIN: IHD 53% vs. control 40%	No benefit
Vogt(134)	RCT	113	SCr 308-316 mol/L	Single session post-IHD vs. Control	*Major event: 24% IHD vs. control 14%	No benefit
Huber(130)	Observational	31	SCr 354 mol/L	Single session post-IHD (no control)	CIN in 61% within 7 days	No benefit
Frank(133)	RCT	17	SCr 345-371 mol/L	Single session peri-procedural IHD vs. Control	CrCl no different at 7 days or need for incident RRT	No benefit
Marenzi (137)	RCT	114	SCr 265-274 mol/L	Pre/post-CVVH (QB 100mL/min, QUF 1L/hr, for 24-30hr) vs. 0.9% NS Control	CIN: 5% CVVH vs. 50% control; mortality: 2% CVVH vs. 14% control	CVVH associated with reduced incidence of CIN and reduced mortality; however, limitations
Hsieh(132)	Retrospective case-control	40	SCr 309-345 mol/L	Single session post-IHD vs. Control	SCr no different at discharge, 3 and 6 months	No benefit
Marenzi(138)	RCT	92	SCr 318-327 mol/L	0.9% NS Control vs. post-CVVH vs. pre/post-CVVH	CIN: 0.9%NS 40%; post-CVVH 26%; pre/post CVVH 3%	CVVH associated with reduced incidence of CIN and need for further RRT; however, limitations

Abbreviations: RCT = randomized controlled trial; CrCl = creatinine clearance; SCr = serum creatinine; IHD = intermittent hemodialysis; CVVH = continuous veno-venous hemofiltration; QB = blood flow rate; QUF = ultrafiltration rate; RRT = renal replacement therapy;
*Major event included: CIN requiring RRT, major cardiovascular event, death or RRT-related complications

media-induced reductions in kidney function.(147)

Interventions with Evidence of No Benefit

Forced diuresis - Furosemide has been hypothesized to reduce the potential for kidney medullary ischemic injury in response to radiocontrast media administration; however, this hypothetical benefit has not been demonstrated in clinical studies.(45, 153) In a randomized controlled trial of 78 patients with chronic kidney disease undergoing cardiac catheterization, Solomon et al. compared hydration alone vs. hydration plus forced diuresis with furosemide and mannitol.(26) The combination of furosemide and mannitol was found to results in a higher incidence of CIN, suggesting forced diuresis might paradoxically worsen kidney function. In a similar randomized controlled study comparing hydration alone vs. hydration plus forced diuresis with furosemide, mannitol and low-dose dopamine, no significant differences in serum creatinine at 48 hours or incidence of CIN was evident.(55) The available evidence has clearly suggested no benefit, and perhaps potential harm for use of a regimen of forced diuresis for prevention of CIN.

Dopamine and fenoldopam (DA1 agonist)- Renal-dose dopamine has long been proposed for prevention of CIN by preserving RBF, GFR, and promoting natriuresis and diuresis. In low doses, dopamine predominantly non-selectively stimulates two families of intra-renal receptor subtypes: DA1 and DA2.(154, 155) DA1 receptors are primarily located in the renal vasculature and proximal tubules where stimulation results in renal vasodilation, natriuresis and diuresis.(156) DA2 receptors have been isolated in the glomerulus, sympathetic pre- and post-synaptic nerve terminals and renal tubules.(156) The physiologic effects of DA2 appear more complex; where stimulation may result in RBF redistribution by inhibition of renin and medullary vasoconstriction.(156)

Prospective clinical trials to date comparing prophylactic dopamine infusions with hydration alone have involved relatively few patients, have been underpowered statistically and have demonstrated no convincing reduction in CIN.(153, 157-160) Two small randomized trials comparing the effects of hydration plus dopamine therapy compared with hypotonic saline hydration alone in high-risk patients referred for cardiac catheterization reported no meaningful reduction in CIN when.(10, 161) In addition, the use of dopamine may worsen kidney function in patients with underlying diabetes mellitus and baseline serum creatinine >177 µmol/L if continued after the development of CIN.(10, 159) Finally, in a large, multi-centre, randomized, placebo-controlled trial of continuous renal-dose dopamine in critically ill patients with evidence of early renal dysfunction, dopamine failed to demonstrate evidence of renal protection or improvement in clinical outcomes.(162) Moreover, renal-dose dopamine may contribute harm by suppressing respiratory drive, inducing tachyarrhythmias or myocardial ischemia, and contributing to metabolic abnormalities, volume depletion and bowel ischemia.(163-165) Given that the current evidence suggests that renal-dose dopamine is not clearly beneficial for the prevention of CIN and that it may be associated with worsened kidney function(166), renal-dose dopamine should not be routinely administered for this indication.

Fenoldopam is a selective DA1 agonist with no affinity for adrenergic DA2, α or β-receptors. It has been shown to reduce systemic vascular resistance while increasing RBF through reversal of the vasoconstrictive effects of angiotensin II and endothelin.(167) Fenoldopam improves both the renal cortical and medullary blood flow, and decreases sodium reabsorption in the proximal tubule.(168) In animal studies, fenoldopam preserves RBF and GFR following radiocontrast media administration.(169) In a pilot study of 45 patients, Tumlin et al. demonstrated a short-term improvement in RBF in patients exposed to a prophylactic fenoldopam infusion during intravascular angiography.(170) However, no difference on the incidence of CIN was demonstrated with fenoldopam compared with placebo. Similarly, Allaqaband et al. found no difference in the incidence of CIN at 48 hours with prophylactic fenoldopam infusion compared with hydration alone.(69) While small non-randomized cohort studies have suggested a benefit with fenoldopam(171-176), a recent large, multicenter, randomized controlled trial of 315 patients with estimated GFR <60 mL/min (mean GFR 29mL/min) undergoing elective cardiac catheterization that compared fenoldopam infusion with placebo for prevention of CIN demonstrated no benefit.(177) The primary outcome was incidence of CIN defined as an increase in baseline serum creatinine >25% at 96 hours following administration. All patients received a hydration protocol. The primary outcome occurred in 33.6% of patients receiving fenoldopam versus 30.1% receiving placebo (p=0.61), with no differences in the secondary outcomes of 30-day mortality, need for RRT, or re-hospitalization. Based on the data from this definitive trial, fenoldopam should not be used for prevention of CIN.

Angiotensin converting enzyme inhibitors – While captopril was hypothesized to ameliorate CIN by reducing in renal medullary ischemia in a small single centre study of 71 diabetic patients referred for cardiac catheterization, without further confirmatory trials this therapy should not be used.(178) ACE inhibitors are generally recognized as precipitants of ARF. Their use may theoretically worsen kidney function if introduced in the setting of a patient with chronic kidney disease referred for an interventional procedure where radiocontrast media will be given.

Atrial natriuretic peptides - Natriuretic peptides, including atrial natriuretic peptide (ANP) secreted principally from the cardiac atria and urodilatin produced locally in the kidney, have both demonstrated renal hemodynamic and tubular actions.(179) Natriuretic peptides have been shown to augment RBF and glomerular perfusion pressure by selective vasodila-

tion of afferent and constriction of efferent arterioles while inducing renal tubular natriuresis through either inhibition of the renin-angiotensin system, inhibition of sodium transport in the inner medullary collecting duct, or antagonizing the action of vasopressin in the cortical collecting tubules.(179) Elevation of serum ANP has been demonstrated following radiocontrast media administration.(180, 181) The increase in serum ANP has been suggested as an adaptive response to the toxic effects of radiocontrast media and counter the renal hemodynamic effects of increased endothelin.(180, 181) ANP was shown to significantly improve GFR and reduce the need for RRT in a randomized trial of 53 patients with ARF when compared with placebo.(182) However, larger trials have not demonstrated similar benefit. In a large trial of 504 critically ill patients with ARF, ANP failed to demonstrate any improvement in dialysis-free survival; however, subgroup analysis suggested a benefit in patients with oliguric ARF.(183) In a test of this hypothesis, a follow-up study of 222 patients with oliguric ARF proved no difference in dialysis-free survival or overall mortality with ANP versus placebo.(184) Finally, a randomized, double-blind, controlled study of 247 patients with stable chronic kidney disease (GFR <60ml/min) compared three doses of ANP infusions with hydration versus hydration alone.(185) There were no significant differences evident for change in serum creatinine or the incidence of CIN with any of the three doses of ANP administration. Based on the data available at present, there is no evidence to recommend the use of ANP or similar analogues for prevention of CIN.

Endothelin receptor antagonists – Endothelin is a potent endogenous vasoconstrictor principally produced by vascular endothelium and a central regulator of renal hemodynamics. Elevation in serum endothelin has been hypothesized to play a contributing role in the pathophysiology of CIN. Elevation in both serum and urinary endothelin concentration has been shown following administration of radiocontrast media.(186-188) Experimental studies have suggested that renal endothelin receptor blockade can prevent and/or ameliorate the reduction in kidney function following radiocontrast media exposure.(189-191) However, Wang et al. reported an increase in CIN in 158 chronic kidney disease patients (mean baseline serum creatinine 242 μmol/L) randomized to receive a mixed endothelin α and β receptor antagonist plus hydration versus hydration alone following cardiac catheterization.(192) At 48 hours, both diabetic and non-diabetic patients receiving endothelin receptor antagonist demonstrated a greater increase in serum creatinine from baseline and a higher incidence of CIN (56% vs. 29%, p=0.002) compared with hydration alone. The evidence available to date suggests that endothelin receptor antagonists should not be administered for the prevention of CIN. Whether future clinical studies will establish a role of selective endothelin receptor antagonists remains unclear.

CONCLUSIONS

CIN remains an important cause for iatrogenic and in-hospital ARF that is associated with increased morbidity and mortality. Several risk factors for CIN have been identified including pre-existing chronic kidney disease, diabetes mellitus, congestive heart failure, concurrent critical illness and volume of administered radiocontrast media. A scoring assessment tool has recently been developed and published to assist in quantifying an individual patient's risk for CIN.

Despite advances in the epidemiology, pathophysiology and natural history of CIN, few effective prophylactic or therapeutic interventions have conclusively demonstrated evidence for a reduction in CIN incidence and no therapy has proven efficacious once CIN is established. At present, prevention of CIN is aimed at identifying patients with risk factors in advance of radiocontrast media exposure. In these patients, in particular those with pre-existing kidney disease or diabetes mellitus, consideration should be given to delaying the diagnostic or interventional procedure until kidney function can be optimised. Likewise, every effort should be made to identify and correct underlying volume depletion and discontinue potential nephrotoxins. During the procedure, a minimum volume of radiocontrast media should be used, including avoiding left venticulograms and performing staged procedures if applicable.

Interventions with evidence for prevention of CIN included peri-procedure hydration and the use of non-ionic iso-osmolar (e.g. iodixanol) radiocontrast media. For those patients at high risk, there is evidence to suggest a benefit with higher dose NAC. Clinical studies with adenosine antagonists, vitamin C and statins are encouraging but require confirmatory trials. Based on the available studies, there is inadequate evidence for the routine use of renal replacement therapy, atrial natriuretic peptides, calcium channel blockers, or prostaglandins. There is no evidence to support prophylaxis with diuretic therapy, forced diuresis, renal-dose dopamine, fenoldopam, captopril, or endothelin receptor antagonists.

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References:

1. Hou S.H., Bushinsky D.A., Wish J.B. et al. Hospital-acquired renal insufficiency: a prospective study. Am. J. Med., 1983,74(2),243-8.

2. Shusterman N., Strom B.L., Murray T.G. et al . Risk factors and outcome of hospital-acquired acute renal failure. Clinical epidemiologic study. Am. J. Med., 1987, 83(1),65-71.

3. Corwin H.L., Teplick R.S., Schreiber M.J. et al. Prediction of outcome in acute renal failure. Am.J.Nephrol., 1987,7(1),8-12.

4. Nash K., Hafeez A., Hou S. Hospital-acquired renal insufficiency. Am.J.Kidney. Dis., 2002,39(5),930-6.
5. Murphy S.W., Barrett B.J., Parfrey P.S. Contrast nephropathy. J. Am.Soc. Nephrol., 2000,11(1),177-82.
6. Kramer B.K., Kammerl M., Schweda F., Schreiber M. A primer in radiocontrast-induced nephropathy. Nephrol. Dial. Transplant., 1999,14(12),2830-4.
7. Gruberg L., Mintz G.S., Mehran R. et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J. Am. Coll. Cardiol., 2000,36(5),1542-8.
8. Levy E.M., Viscoli C.M., Horwitz R.I. The effect of acute renal failure on mortality. A cohort analysis. JAMA, 1996,275(19),1489-94.
9. Powe N.R., Moore R.D., Steinberg E.P. Adverse reactions to contrast media: factors that determine the cost of treatment. Am.J.Roentgenol., 1993, 161(5), 1089-95.
10. Abizaid A.S., Clark C.E., Mintz G.S. et al. Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency. Am.J.Cardiol., 1999,83(2),260-3, A5.
11. Rudnick M.R., Berns J.S., Cohen R.M., Goldfarb S. Nephrotoxic risks of renal angiography: contrast media-associated nephrotoxicity and atheroembolism—a critical review. Am.J.Kidney Dis., 1994,24(4),713-27.
12. Saklayen M.G., Gupta S., Suryaprasad A., Azmeh W. Incidence of atheroembolic renal failure after coronary angiography. A prospective study. Angiology, 1997, 48(7),609-13.
13. Keeley E.C., Grines C.L. Scraping of aortic debris by coronary guiding catheters: a prospective evaluation of 1,000 cases. J.Am.Coll.Cardiol., 1998,32(7),1861-5.
14. Barrett B.J. Contrast nephrotoxicity. J. Am. Soc. Nephrol., 1994,5(2),125-37.
15. Rihal C.S., Textor S.C., Grill D.E. et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation, 2002, 105(19),2259-64.
16. Lindsay J., Apple S., Pinnow E.E. et al. Percutaneous coronary intervention-associated nephropathy foreshadows increased risk of late adverse events in patients with normal baseline serum creatinine. Catheter. Cardiovasc. Interv., 2003,59(3),338-43.
17. Fang L.S., Sirota R.A., Ebert T.H., Lichtenstein N.S. Low fractional excretion of sodium with contrast media-induced acute renal failure. Arch. Intern .Med., 1980, 140(4),531-3.
18. D'Elia J.A., Gleason R.E., Alday M. et al. Nephrotoxicity from angiographic contrast material. A prospective study. Am.J.Med., 1982,72(5),719-25.
19. Weinrauch L.A., Healy R.W., Leland O.S., Jr.. et al. Coronary angiography and acute renal failure in diabetic azotemic nephropathy. Ann. Intern. Med., 1977, 86(1),56-9.
20. Carraro M., Mancini W., Artero M. et al. Dose effect of nitrendipine on urinary enzymes and microproteins following non-ionic radiocontrast administration. Nephrol. Dial. Transplant., 1996, 11(3), 444-8.
21. Rudnick M.R., Goldfarb S., Wexler L. et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. The Iohexol Cooperative Study. Kidney Int. ,1995, 47(1),254-61.
22. Sterner G., Nyman U., Valdes T. Low risk of contrast-medium-induced nephropathy with modern angiographic technique. J. Intern. Med., 2001, 250(5), 429-34.
23. Rudnick M.R., Goldfarb S. Pathogenesis of contrast-induced nephropathy: experimental and clinical observations with an emphasis on the role of osmolality. Rev. Cardiovasc.Med., 2003,4, Suppl 5,S28-33.
24. Quader M.A., Sawmiller C., Sumpio B.A. Contrast-induced nephropathy: review of incidence and pathophysiology. Ann. Vasc. Surg., 1998,12(6),612-20.
25. McCullough P.A., Soman S.S. Contrast-induced nephropathy. Crit. Care. Clin., 2005,21(2),261-80.
26. Solomon R., Werner C., Mann D. et al. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N. Engl. J. Med., 1994,331(21),1416-20.
27. McCullough P.A., Wolyn R., Rocher L.L. et al. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am.J.Med., 1997, 103(5),368-75.
28. Mueller C., Seidensticker P., Buettner H.J. et al. Incidence of contrast nephropathy in patients receiving comprehensive intravenous and oral hydration. Swiss Med. Wkly, 2005,135(19-20),286-90.
29. Katholi R.E., Taylor G.J., McCann W.P. et al. Nephrotoxicity from contrast media: attenuation with theophylline. Radiology, 1995,195(1),17-22.
30. Davidson C.J., Hlatky M., Morris K.G. et al. Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization. A prospective trial. Ann. Intern. Med., 1989,110(2),119-24.
31. Rich M.W., Crecelius C.A. Incidence, risk factors, and clinical course of acute renal insufficiency after cardiac catheterization in patients 70 years of age or older. A prospective study. Arch. Intern. Med., 1990;150(6):1237-42.
32. Guitterez N.V., Diaz A., Timmis G.C. et al. Determinants of serum creatinine trajectory in acute contrast nephropathy. J. Interv. Cardiol., 2002,15(5),349-54.
33. Cigarroa R.G., Lange R.A., Williams R.H., Hillis L.D. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. Am.J.Med., 1989, 86(6 Pt 1),649-52.
34. Albert S.G., Shapiro M.J., Brown W.W. et al. Analysis of radiocontrast-induced nephropathy by dual-labeled radionuclide clearance. Invest. Radiol., 1994, 29(6), 618-23.
35. Moore R.D., Steinberg E.P., Powe N.R. et al. Frequency and determinants of adverse reactions induced by high-osmolality contrast media. Radiology, 1989,170(3 Pt 1),727-32.
36. McCullough P.A., Sandberg K.R. Epidemiology of contrast-induced nephropathy. Rev. Cardiovasc. Med., 2003,4, Suppl 5,S3-9.
37. Manske C.L., Sprafka J.M., Strony J.T., Wang Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. Am.J.Med., 1990, 89(5),615-20.
38. Iakovou I., Dangas G., Mehran R. et al. Impact of gender on the incidence and outcome of contrast-induced nephropathy after percutaneous coronary intervention. J. Invasive Cardiol., 2003,15(1),18-22.
39. Mehran R., Aymong E.D., Nikolsky E. et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J.Am.Coll.Cardiol., 2004,44(7),1393-9.

40. Allgren R.L. Update on clinical trials with atrial natriuretic peptide in acute tubular necrosis. Ren. Fail., 1998,20(5),691-5.
41. Lautin E.M., Freeman N.J., Schoenfeld A.H. et al. Radiocontrast-associated renal dysfunction: incidence and risk factors. Am.J.Roentgenol., 1991,157(1),49-58.
42. Huber W., Ilgmann K., Page M. et al. Effect of theophylline on contrast material-nephropathy in patients with chronic renal insufficiency: controlled, randomized, double-blinded study. Radiology, 2002,223(3),772-9.
43. Holt S., Goodier D., Marley R. et al. Improvement in renal function in hepatorenal syndrome with N-acetylcysteine. Lancet, 1999,353(9149),294-5.
44. Najjar M., Hamad A., Salameh M. et al. The risk of radiocontrast nephropathy in patients with cirrhosis. Ren. Fail., 2002,24(1),11-8.
45. Weinstein J.M., Heyman S., Brezis M. Potential deleterious effect of furosemide in radiocontrast nephropathy. Nephron, 1992,62(4),413-5.
46. Cohen D.J., Sherman W.H., Osserman E.F., Appel G.B. Acute renal failure in patients with multiple myeloma. Am.J.Med., 1984,76(2),247-56.
47. McCarthy C.S., Becker J.A. Multiple myeloma and contrast media. Radiology, 1992,183(2),519-21.
48. Parfrey P.S., Griffiths S.M., Barrett B.J. et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. N.Engl.J.Med., 1989,320(3),143-9.
49. Gruberg L, Mehran R, Dangas G. et al. Acute renal failure requiring dialysis after percutaneous coronary interventions. Catheter Cardiovasc Interv. 2001;52(4):409-16.
50. Freeman R.V., O'Donnell M., Share D. et al. Nephropathy requiring dialysis after percutaneous coronary intervention and the critical role of an adjusted contrast dose. Am.J.Cardiol., 2002,90(10),1068-73.
51. Bagshaw S.M., Culleton B.F. Acetylcysteine and renal function following coronary angiographic procedures. JAMA, 2003,289(21),2795; author reply 2796.
52. Hoffmann U., Banas B., Fischereder M., Kramer B.K. N-acetylcysteine in the prevention of radiocontrast-induced nephropathy: clinical trials and end points. Kidney Blood Press. Res., 2004,27(3),161-6.
53. Eisenberg R.L., Bank W.O., Hedgcock M.W. Renal failure after major angiography. Am.J.Med., 1980,68(1),43-6.
54. Eisenberg R.L., Bank W.O., Hedgock M.W. Renal failure after major angiography can be avoided with hydration. Am.J.Roentgenol., 1981,136(5),859-61.
55. Stevens M.A., McCullough P.A., Tobin K.J. et al. A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the P.R.I.N.C.E. Study. Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation. J.Am.Coll.Cardiol., 1999,33(2),403-11.
56. Taylor A.J., Hotchkiss D., Morse R.W., McCabe J. PREPARED: Preparation for Angiography in Renal Dysfunction: a randomized trial of inpatient vs outpatient hydration protocols for cardiac catheterization in mild-to-moderate renal dysfunction. Chest, 1998,114(6),1570-4.
57. Trivedi H.S., Moore H., Nasr S. et al. A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. Nephron. Clin. Pract., 2003,93(1),C29-34.
58. Bader B.D., Berger E.D., Heede M. Fluid administration: When and how much to prevent contrast media nephrotoxicity (Abstract). J. Am. Soc. Nephrol., 2002, 11, 125A.
59. Mueller C., Buerkle G., Buettner H.J. et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch. Intern. Med., 2002, 162(3), 329-36.
60. Merten G.J., Burgess W.P., Gray L.V. et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. JAMA, 2004,291(19),2328-34.
61. Barrett B.J., Carlisle E.J. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. Radiology, 1993,188(1),171-8.
62. Moore R.D., Steinberg E.P., Powe N.R. et al. Nephrotoxicity of high-osmolality versus low-osmolality contrast media: randomized clinical trial. Radiology, 1992,182(3),649-55.
63. Aspelin P., Aubry P., Fransson S.G. et al. Nephrotoxic effects in high-risk patients undergoing angiography. N.Engl.J.Med., 2003,348(6),491-9.
64. Kelly G.S. Clinical applications of N-acetylcysteine. Altern. Med. Rev., 1998, 3(2),114-27.
65. Yoshioka T., Fogo A., Beckman J.K. Reduced activity of antioxidant enzymes underlies contrast media-induced renal injury in volume depletion. Kidney Int., 1992,41(4),1008-15.
66. DiMari J., Megyesi J., Udvarhelyi N. et al. N-acetyl cysteine ameliorates ischemic renal failure. Am.J.Physiol., 1997,272(3 Pt 2),F292-8.
67. Drager L.F., Andrade L., Barros de Toledo J.F. et al. Renal effects of N-acetylcysteine in patients at risk for contrast nephropathy: decrease in oxidant stress-mediated renal tubular injury. Nephrol. Dial. Transplant., 2004,19(7),1803-7.
68. Tepel M., van der Giet M., Schwarzfeld C. et al. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N.Engl.J.Med., 2000,343(3),180-4.
69. Allaqaband S., Tumuluri R., Malik A.M. et al. Prospective randomized study of N-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy. Catheter. Cardiovasc.Interv., 2002,57(3),279-83.
70. Baker C.S., Wragg A., Kumar S. et al. A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID study. J.Am.Coll.Cardiol., 2003,41(12),2114-8.
71. Briguori C., Manganelli F., Scarpato P. et al. Acetylcysteine and contrast agent-associated nephrotoxicity. J.Am.Coll.Cardiol., 2002,40(2),298-303.
72. Briguori C., Colombo A., Violante A. et al. Standard vs double dose of N-acetylcysteine to prevent contrast agent associated nephrotoxicity. Eur. Heart J., 2004,25(3),206-11.
73. Durham J.D., Caputo C., Dokko J. et al. A randomized controlled trial of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography. Kidney Int., 2002,62(6),2202-7.
74. Efrati S., Dishy V., Averbukh M. et al. The effect of N-acetylcysteine on renal function, nitric oxide, and oxidative stress after angiography. Kidney Int., 2003, 64(6), 2182-7.
75. Fung J.W., Szeto C.C., Chan W.W. et al. Effect of N-acetylcysteine for prevention of contrast nephropathy in patients with moderate to severe renal insufficiency: a randomized trial. Am.J.Kidney Dis., 2004,43(5),801-8.
76. Goldenberg I., Shechter M., Matetzky S. et al. Oral acetylcysteine as an adjunct to saline hydration for the prevention of contrast-induced nephropathy following coronary angiography.

A randomized controlled trial and review of the current literature. Eur. Heart J., 2004,25(3),212-8.
77. Kay J., Chow W.H., Chan T.M. et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. JAMA, 2003,289(5),553-8.
78. MacNeill B.D., Harding S.A., Bazari H. et al. Prophylaxis of contrast-induced nephropathy in patients undergoing coronary angiography. Catheter. Cardiovasc. Interv., 2003, 60(4), 458-61.
79. Ochoa A., Pellizzon G., Addala S. et al. Abbreviated dosing of N-acetylcysteine prevents contrast-induced nephropathy after elective and urgent coronary angiography and intervention. J. Interv. Cardiol., 2004,17(3),159-65.
80. Oldemeyer J.B., Biddle W.P. Wurdeman R.L. et al . Acetylcysteine in the prevention of contrast-induced nephropathy after coronary angiography. Am. Heart J., 2003,146(6),E23.
81. Shyu K.G., Cheng J.J., Kuan P. Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure. J.Am. Coll.Cardiol., 2002,40(8),1383-8.
82. Vallero A., Cesano G., Pozzato M. et al. [Contrast nephropathy in cardiac procedures: no advantages with prophylactic use of N-acetylcysteine (NAC)]. G. Ital. Nefrol., 2002,19(5),529-33.
83. Diaz-Sandoval L.J., Kosowsky B.D., Losordo D.W. Acetylcysteine to prevent angiography-related renal tissue injury (the APART trial). Am.J.Cardiol., 2002, 89(3),356-8.
84. Boccalandro F., Amhad M., Smalling R.W., Sdringola S. Oral acetylcysteine does not protect renal function from moderate to high doses of intravenous radiographic contrast. Catheter. Cardiovasc. Interv., 2003,58(3),336-41.
85. Azmus A.D., Gottschall C., Manica A. et al. Effectiveness of acetylcysteine in prevention of contrast nephropathy. J. Invasive Cardiol., 2005,17(2),80-4.
86. Gomes V.O., Poli de Figueredo C.E., Caramori P. et al. N-acetylcysteine does not prevent contrast induced nephropathy after cardiac catheterisation with an ionic low osmolality contrast medium: a multicentre clinical trial. Heart, 2005, 91(6), 774-8.
87. Miner S.E., Dzavik V., Nguyen-Ho P. et al. N-acetylcysteine reduces contrast-associated nephropathy but not clinical events during long-term follow-up. Am. Heart J., 2004,148(4),690-5.
88. Briguori C., Colombo A., Airoldi F. et al. N-Acetylcysteine versus fenoldopam mesylate to prevent contrast agent-associated nephrotoxicity. J.Am.Coll.Cardiol., 2004,44(4),762-5.
89. Kefer J.M., Hanet C.E., Boitte S. et al. Acetylcysteine, coronary procedure and prevention of contrast-induced worsening of renal function: which benefit for which patient? Acta Cardiol., 2003,58(6),555-60.
90. Webb J.G., Pate G.E., Humphries K.H. et al. A randomized controlled trial of intravenous N-acetylcysteine for the prevention of contrast-induced nephropathy after cardiac catheterization: lack of effect. Am. Heart J., 2004,148(3),422-9.
91. Hoffmann U., Fischereder M., Kruger B. et al. The value of N-acetylcysteine in the prevention of radiocontrast agent-induced nephropathy seems questionable. J. Am. Soc. Nephrol., 2004,15(2),407-10.
92. Curhan G.C. Prevention of contrast nephropathy. JAMA, 2003,289(5),606-8.
93. Birck R., Krzossok S., Markowetz F. et al. Acetylcysteine for prevention of contrast nephropathy: meta-analysis. Lancet, 2003,362(9384),598-603.
94. Guru V., Fremes S.E. The role of N-acetylcysteine in preventing radiographic contrast-induced nephropathy. Clin. Nephrol., 2004,62(2),77-83.
95. Nallamothu B.K., Shojania K.G., Saint S. et al. Is acetylcysteine effective in preventing contrast-related nephropathy? A meta-analysis. Am.J.Med., 2004, 117(12),938-47.
96. Misra D., Leibowitz K., Gowda R.M. et al. Role of N-acetylcysteine in prevention of contrast-induced nephropathy after cardiovascular procedures: a meta-analysis. Clin. Cardiol., 2004,27(11),607-10.
97. Liu R., Nair D., Ix J. et al. N-acetylcysteine for the prevention of contrast-induced nephropathy. A systematic review and meta-analysis. J.Gen.Intern. Med., 2005, 20(2),193-200.
98. Kshirsagar A.V., Poole C., Mottl A. et al. N-acetylcysteine for the prevention of radiocontrast induced nephropathy: a meta-analysis of prospective controlled trials. J. Am. Soc. Nephrol., 2004,15(3),761-9.
99. Isenbarger D.W., Kent S.M., O'Malley P.G. Meta-analysis of randomized clinical trials on the usefulness of acetylcysteine for prevention of contrast nephropathy. Am.J.Cardiol., 2003, 92(12),1454-8.
100. Bagshaw S.M., Ghali W.A. Acetylcysteine for prevention of contrast-induced nephropathy after intravascular angiography: a systematic review and meta-analysis. BMC Med., 2004,2,38.
101. Pannu N., Manns B., Lee H., Tonelli M. Systematic review of the impact of N-acetylcysteine on contrast nephropathy. Kidney Int., 2004,65(4),1366-74.
102. Briguori C., Colombo A., Airoldi F. et al. Nephrotoxicity of low-osmolality versus iso-osmolality contrast agents: Impact of N-acetylcysteine. Kidney Int., 2005, 68(5), 2250-5.
103. Bagshaw S.M., McAlister F.A., Manns B.J., Ghali W.A. Acetylcysteine in the prevention of contrast-induced nephropathy. A case study of the pitfalls in the evolution of evidence. Arch. Intern. Med., 2005:In Press.
104. Spargias K., Alexopoulos E., Kyrzopoulos S. et al. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. Circulation, 2004,110(18),2837-42.
105. Canavese C., Petrarulo M., Massarenti P. et al. Long-term, low-dose, intravenous vitamin C leads to plasma calcium oxalate supersaturation in hemodialysis patients. Am.J.Kidney Dis., 2005,45(3),540-9.
106. Haeussler U., Riedel M., Keller F. Free reactive oxygen species and nephrotoxicity of contrast agents. Kidney Blood Press. Res., 2004,27(3),167-71.
107. Bellosta S., Ferri N., Arnaboldi L. et al. Pleiotropic effects of statins in atherosclerosis and diabetes. Diabetes Care, 2000,23, Suppl 2,B72-8.
108. Attallah N., Yassine L., Musial J. et al. The potential role of statins in contrast nephropathy. Clin. Nephrol., 2004,62(4),273-8.
109. Khanal S., Attallah N., Smith D.E. et al. Statin therapy reduces contrast-induced nephropathy: an analysis of contemporary percutaneous interventions. Am.J.Med., 2005,118(8),843-9.

110. O'Connor A.S., Love T.E. Propensity scores and observational research. Am.J.Med., 2006,119(3),e15-6; author reply e17-8.
111. Spielman W.S., Arend L.J. Adenosine receptors and signalling in the kidney. Hypertension, 1991,17(2),117-30.
112. Arakawa K., Suzuki H., Naitoh M. et al. Role of adenosine in the renal responses to contrast medium. Kidney Int., 1996,49(5),1199-206.
113. Arend L.J., Bakris G.L., Burnett J.C. Jr. et al. Role for intrarenal adenosine in the renal hemodynamic response to contrast media. J. Lab. Clin. Med., 1987, 110(4) 406-11.
114. Deray G., Martinez F., Cacoub P. et al. A role for adenosine calcium and ischemia in radiocontrast-induced intrarenal vasoconstriction. Am.J.Nephrol., 1990,10(4),316-22.
115. Oldroyd S.D., Fang L., Haylor J.L. et al. Effects of adenosine receptor antagonists on the responses to contrast media in the isolated rat kidney. Clin. Sci. (Lond)., 2000,98(3),303-11.
116. Gandhi M.R., Brown P., Romanowski C.A. et al. The use of theophylline, an adenosine antagonist in the prevention of contrast media induced nephrotoxicity. Br. J. Radiol., 1992,65(777),838.
117. Erley C.M., Duda S.H., Schlepckow S. et al. Adenosine antagonist theophylline prevents the reduction of glomerular filtration rate after contrast media application. Kidney Int., 1994,45(5),1425-31.
118. Erley C.M., Heyne N., Burgert K. et al. Prevention of radiocontrast-induced nephropathy by adenosine antagonists in rats with chronic nitric oxide deficiency. J. Am. Soc. Nephrol., 1997,8(7),1125-32.
119. Kapoor A., Kumar S., Gulati S. et al. The role of theophylline in contrast-induced nephropathy: a case-control study. Nephrol. Dial. Transplant., 2002,17(11),1936-41.
120. Huber W., Schipek C., Ilgmann K. et al. Effectiveness of theophylline prophylaxis of renal impairment after coronary angiography in patients with chronic renal insufficiency. Am.J.Cardiol., 2003,91(10),1157-62.
121. Shammas N.W., Kapalis M.J., Harris M. et al. Aminophylline does not protect against radiocontrast nephropathy in patients undergoing percutaneous angiographic procedures. J. Invasive Cardiol., 2001,13(11),738-40.
122. Kolonko A., Wiecek A., Kokot F. The nonselective adenosine antagonist theophylline does prevent renal dysfunction induced by radiographic contrast agents. J. Nephrol., 1998,11(3),151-6.
123. Erley C.M., Duda S.H., Rehfuss D. et al. Prevention of radiocontrast-media-induced nephropathy in patients with preexisting renal insufficiency by hydration in combination with the adenosine antagonist theophylline. Nephrol. Dial. Transplant., 1999,14(5),1146-9.
124. Ix J.H., McCulloch C.E., Chertow G.M. Theophylline for the prevention of radiocontrast nephropathy: a meta-analysis. Nephrol. Dial. Transplant., 2004, 19(11), 2747-53.
125. Bagshaw S.M., Ghali W.A. Theophylline for prevention of contrast-induced nephropathy: a systematic review and meta-analysis. Arch. Intern. Med., 2005, 165(10), 1087-93.
126. Moon S.S., Back S.E., Kurkus J., Nilsson-Ehle P. Hemodialysis for elimination of the nonionic contrast medium iohexol after angiography in patients with impaired renal function. Nephron, 1995,70(4),430-7.
127. Schindler R., Stahl C., Venz S. et al. Removal of contrast media by different extracorporeal treatments. Nephrol. Dial. Transplant., 2001,16(7),1471-4.
128. Sterner G., Frennby B., Kurkus J., Nyman U. Does post-angiographic hemodialysis reduce the risk of contrast-medium nephropathy? Scand. J. Urol. Nephrol., 2000,34(5),323-6.
129. Berger E.D., Bader B.D., Bosker J. et al. [Contrast media-induced kidney failure cannot be prevented by hemodialysis]. Dtsch. Med. Wochenschr., 2001, 126(7), 162-6.
130. Huber W., Jeschke B., Kreymann B. et al. Haemodialysis for the prevention of contrast-induced nephropathy: outcome of 31 patients with severely impaired renal function, comparison with patients at similar risk and review. Invest. Radiol., 2002, 37(9),471-81.
131. Lehnert T., Keller E., Gondolf K., et al. Effect of haemodialysis after contrast medium administration in patients with renal insufficiency. Nephrol. Dial. Transplant., 1998,13(2),358-62.
132. Hsieh Y.C., Ting C.T., Liu T.J. et al. Short- and long-term renal outcomes of immediate prophylactic hemodialysis after cardiovascular catheterizations in patients with severe renal insufficiency. Int. J. Cardiol., 2005,101(3),407-13.
133. Frank H., Werner D., Lorusso V. et al. Simultaneous hemodialysis during coronary angiography fails to prevent radiocontrast-induced nephropathy in chronic renal failure. Clin. Nephrol., 2003,60(3),176-82.
134. Vogt B., Ferrari P., Schonholzer C. et al. Prophylactic hemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful. Am.J.Med., 2001,111(9),692-8.
135. Younathan C.M., Kaude J.V., Cook M.D. et al. Dialysis is not indicated immediately after administration of nonionic contrast agents in patients with end-stage renal disease treated by maintenance dialysis. Am.J.Roentgenol., 1994, 163(4), 969-71.
136. Marenzi G., Marana I., Lauri G. et al. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. N.Engl.J.Med., 2003,349(14),1333-40.
137. Marenzi G., Bartorelli A.L. Hemofiltration in the prevention of radiocontrast agent induced nephropathy. Minerva Anestesiol., 2004,70(4),189-91.
138. Marenzi G., Lauri G., Campodonico J. et al. Comparison of two hemofiltration protocols for prevention of contrast-induced nephropathy in high-risk patients. Am.J.Med., 2006,119(2),155-62.
139. Marenzi G., Lauri G., Grazi M. et al. Circulatory response to fluid overload removal by extracorporeal ultrafiltration in refractory congestive heart failure. J.Am.Coll.Cardiol., 2001,38(4),963-8.
140. Tobimatsu M., Konomi K., Saito S., Tsumagari T. Protective effect of prostaglandin E1 on ischemia-induced acute renal failure in dogs. Surgery, 1985,98(1),45-53.
141. Paller M.S., Manivel J.C. Prostaglandins protect kidneys against ischemic and toxic injury by a cellular effect. Kidney Int., 1992,42(6),1345-54.
142. Cantley L.G., Spokes K., Clark B. et al. Role of endothelin and prostaglandins in radiocontrast-induced renal artery constriction. Kidney Int.,1993,44(6),1217-23.
143. Koch J.A., Sketch M., Brinker J., Bernink P.J. [Prostaglandin E1 for prevention of contrast medium-induced kidney dysfunction]. Rofo, 1999,170(6),557-63.

144. Sketch M.H., Jr., Whelton A., Schollmayer E. et al. Prevention of contrast media-induced renal dysfunction with prostaglandin E1: a randomized, double-blind, placebo-controlled study. Am.J.Ther., 2001,8(3),155-62.
145. Duan S.B., Liu F.Y., Luo J.A. et al. Nephrotoxicity of high- and low-osmolar contrast media. The protective role of amlodipine in a rat model. Acta Radiol., 2000,41(5),503-7.
146. Wang Y.X., Jia Y.F., Chen K.M., Morcos S.K. Radiographic contrast media induced nephropathy: experimental observations and the protective effect of calcium channel blockers. Br. J. Radiol., 2001,74(888),1103-8.
147. Esnault V.L. Radiocontrast media-induced nephrotoxicity in patients with renal failure: rationale for a new double-blind, prospective, randomized trial testing calcium channel antagonists. Nephrol. Dial. Transplant., 2002,17(8),1362-4.
148. Cacoub P., Deray G., Baumelou A., Jacobs C. No evidence for protective effects of nifedipine against radiocontrast-induced acute renal failure. Clin. Nephrol., 1988,29(4),215-6.
149. Neumayer H.H., Junge W., Kufner A., Wenning A. Prevention of radiocontrast-media-induced nephrotoxicity by the calcium channel blocker nitrendipine: a prospective randomised clinical trial. Nephrol. Dial. Transplant., 1989, 4(12), 1030-6.
150. Russo D., Testa A., Della Volpe L., Sansone G. Randomised prospective study on renal effects of two different contrast media in humans: protective role of a calcium channel blocker. Nephron, 1990,55(3),254-7.
151. Spangberg-Viklund B., Berglund J., Nikonoff T. et al. Does prophylactic treatment with felodipine, a calcium antagonist, prevent low-osmolar contrast-induced renal dysfunction in hydrated diabetic and nondiabetic patients with normal or moderately reduced renal function? Scand. J. Urol. Nephrol., 1996,30(1),63-8.
152. Khoury Z., Schlicht J.R., Como J. et al. The effect of prophylactic nifedipine on renal function in patients administered contrast media. Pharmacotherapy, 1995,15(1),59-65.
153. Hall K.A., Wong R.W., Hunter G.C. et al. Contrast-induced nephrotoxicity: the effects of vasodilator therapy. J. Surg. Res., 1992,53(4),317-20.
154. Bellomo R., Ronco C. The renal effects of noradrenaline and dopamine. Contrib. Nephrol., 2001, 132,146-57.
155. Denton M.D., Chertow G.M., Brady H.R. «Renal-dose» dopamine for the treatment of acute renal failure: scientific rationale, experimental studies and clinical trials. Kidney Int., 1996,50(1),4-14.
156. Emilien G., Maloteaux J.M., Geurts M. et al. Dopamine receptors—physiological understanding to therapeutic intervention potential. Pharmacol. Ther., 1999, 84(2), 133-56.
157. Hans B., Hans S.S., Mittal V.K. et al. Renal functional response to dopamine during and after arteriography in patients with chronic renal insufficiency. Radiology.,1990,176(3),651-4.
158. Hans S.S., Hans B.A., Dhillon R. et al. Effect of dopamine on renal function after arteriography in patients with pre-existing renal insufficiency. Am. Surg., 1998, 64(5), 432-6.
159. Weisberg L.S., Kurnik P.B., Kurnik B.R. Dopamine and renal blood flow in radiocontrast-induced nephropathy in humans. Ren. Fail., 1993,15(1),61-8.
160. Kapoor A., Sinha N., Sharma R.K. et al. Use of dopamine in prevention of contrast induced acute renal failure—a randomised study. Int. J. Cardiol., 1996,53(3),233-6.
161. Gare M., Haviv Y.S., Ben-Yehuda A. et al. The renal effect of low-dose dopamine in high-risk patients undergoing coronary angiography. J.Am.Coll.Cardiol., 1999, 34(6), 1682-8.
162. Bellomo R., Chapman M., Finfer S. et al. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet, 2000,356(9248),2139-43.
163. Thompson B.T., Cockrill B.A. Renal-dose dopamine: a siren song? Lancet, 1994, 344(8914),7-8.
164. Lee M.R. Dopamine and the kidney. Clin. Sci. (Lond)., 1982,62(5),439-48.
165. Lee M.R. Dopamine and the kidney: ten years on. Clin. Sci. (Lond)., 1993, 84(4), 357-75.
166. Chertow G.M., Sayegh M.H., Allgren R.L., Lazarus J.M. Is the administration of dopamine associated with adverse or favorable outcomes in acute renal failure? Auriculin Anaritide Acute Renal Failure Study Group. Am.J.Med., 1996, 101(1), 49-53.
167. Nichols A.J, Ruffolo R.R., Jr., Brooks D.P. The pharmacology of fenoldopam. Am.J.Hypertens., 1990,3 (6 Pt 2),116S-119S.
168. Mathur V.S., Swan S.K., Lambrecht L.J. et al. The effects of fenoldopam, a selective dopamine receptor agonist, on systemic and renal hemodynamics in normotensive subjects. Crit. Care Med.,1999,27(9),1832-7.
169. Bakris G.L., Lass N.A., Glock D. Renal hemodynamics in radiocontrast medium-induced renal dysfunction: A role for dopamine-1 receptors. Kidney Int., 1999, 56(1), 206-10.
170. Tumlin J.A., Wang A., Murray P.T., Mathur V.S. Fenoldopam mesylate blocks reductions in renal plasma flow after radiocontrast dye infusion: a pilot trial in the prevention of contrast nephropathy. Am. Heart J., 2002,143(5),894-903.
171. Kini A.A., Sharma S.K. Managing the high-risk patient: experience with fenoldopam, a selective dopamine receptor agonist, in prevention of radiocontrast nephropathy during percutaneous coronary intervention. Rev. Cardiovasc. Med., 2001,2. Suppl 1,S19-25.
172. Kini A.S., Mitre C.A., Kamran M. et al. Changing trends in incidence and predictors of radiographic contrast nephropathy after percutaneous coronary intervention with use of fenoldopam. Am.J.Cardiol., 2002,89(8),999-1002.
173. Kini A.S., Mitre C.A., Kim M. et al. A protocol for prevention of radiographic contrast nephropathy during percutaneous coronary intervention: effect of selective dopamine receptor agonist fenoldopam. Catheter. Cardiovasc. Interv., 2002, 55(2),169-73.
174. Madyoon H. Clinical experience with the use of fenoldopam for prevention of radiocontrast nephropathy in high-risk patients. Rev. Cardiovasc. Med., 2001,2 Suppl 1, S26-30.
175. Madyoon H., Croushore L. Use of fenoldopam for prevention of radiocontrast nephropathy in the cardiac catheterization laboratory: a case series. J. Interv. Cardiol., 2001,14(2):179-85.
176. Madyoon H., Croushore L., Weaver D., Mathur V. Use of fenoldopam to prevent radiocontrast nephropathy in high-risk patients. Catheter. Cardiovasc. Interv., 2001,53(3),341-5.
177. Stone G.W., McCullough P.A., Tumlin J.A. et al. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. JAMA, 2003,290(17),2284-91.

178. Gupta R.K., Kapoor A., Tewari S.et al. Captopril for prevention of contrast-induced nephropathy in diabetic patients: a randomised study. Indian Heart J., 1999,51(5),521-6.
179. Levin E.R., Gardner D.G., Samson W.K. Natriuretic peptides. N.Engl.J.Med., 1998,339(5),321-8.
180. Kurnik B.R., Weisberg L.S., Askenase A.D., Kurnik P.B. Mannitol stimulates atrial natriuretic peptide release in humans. Am.J.Kidney Dis., 1991,17(1),62-8.
181. Clark B.A., Kim D., Epstein F.H. Endothelin and atrial natriuretic peptide levels following radiocontrast exposure in humans. Am.J.Kidney Dis., 1997,30(1),82-6.
182. Rahman S.N., Kim G.E., Mathew A.S. et al. Effects of atrial natriuretic peptide in clinical acute renal failure. Kidney Int., 1994,45(6),1731-8.
183. Allgren R.L., Marbury T.C., Rahman S.N. et al. Anaritide in acute tubular necrosis. Auriculin Anaritide Acute Renal Failure Study Group. N.Engl.J.Med., 1997,336(12),828-34.
184. Lewis J., Salem M.M., Chertow G.M. et al. Atrial natriuretic factor in oliguric acute renal failure. Anaritide Acute Renal Failure Study Group. Am.J.Kidney Dis., 2000, 36(4), 767-74.
185. Kurnik B.R., Allgren R.L., Genter F.C. et al. Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. Am.J.Kidney Dis., 1998,31(4),674-80.
186. Heyman S.N,, Clark B.A., Kaiser N. et al. Radiocontrast agents induce endothelin release in vivo and in vitro. J. Am. Soc. Nephrol., 1992,3(1),58-65.
187. Heyman S.N., Clark B.A., Cantley L. et al. Effects of ioversol versus iothalamate on endothelin release and radiocontrast nephropathy. Invest. Radiol., 1993, 28(4), 313-8.
188. Fujisaki K., Kubo M., Masuda K. et al. Infusion of radiocontrast agents induces exaggerated release of urinary endothelin in patients with impaired renal function. Clin. Exp. Nephrol., 2003,7(4),279-83.
189. Oldroyd S.D., Haylor J.L., Morcos S.K. Bosentan, an orally active endothelin antagonist: effect on the renal response to contrast media. Radiology, 1995, 196(3),661-5.
190. Brooks D.P, DePalma P.D. Blockade of radiocontrast-induced nephrotoxicity by the endothelin receptor antagonist, SB 209670. Nephron, 1996,72(4),629-36.
191. Pollock D.M., Polakowski J.S., Wegner C.D., Opgenorth T.J. Beneficial effect of ETA receptor blockade in a rat model of radiocontrast-induced nephropathy. Ren. Fail., 1997,19(6),753-61.
192. Wang A., Holcslaw T., Bashore T.M. et al. Exacerbation of radiocontrast nephrotoxicity by endothelin receptor antagonism. Kidney Int., 2000,57(4),1675-80.

Possible Ways to Improve Treatment Tactics in Acute Myocaridal Infarction

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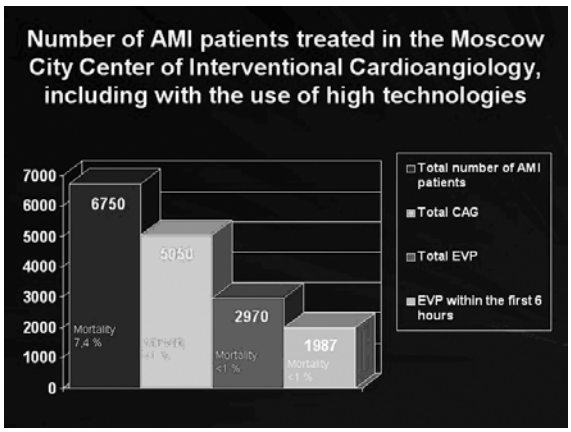
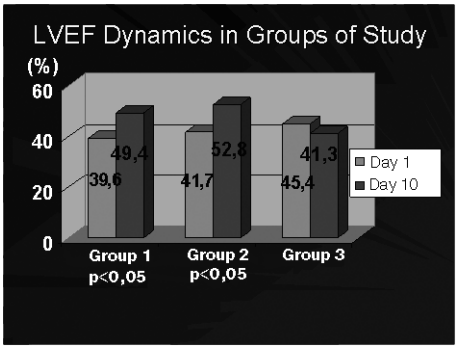
Moscow City Center of Interventional Cardioangiology, which will be 10 in the current year, has an experience with hospital treatment of over 6000 patients with acute myocardial infarction (AMI), of these 4958 underwent selective coronary angiography and left ventriculography, and 4757 – PTCA of the infarct-related artery, in some instances accompanied by intervention in other coronary arteries. In 1987 patients the procedure was performed within the first 6 hours after infarction. Intra- and perioperative mortality was < 1%.

For the last few years hospital mortality due to acute myocardial infarction in the Center has been 4% or lower. We believe that such decrease of mortality rate is mostly due to the extensive use of endovascular diagnostic and interventional procedures in clinical practice.

The experience acquired during these years gives us the right to present our vision of the possible ways to improve therapy for AMI to the audience. Below is the brief strategy of diagnostic and interventional procedures in patients with AMI at pre-hospital stage and during hospital stay.

Despite the obvious success in diagnosis and treatment of AMI , there're still many issues to be resolved and fulfilled. **This applies particularly to the treatment options, which proved effective, but haven't been extensively adopted in Russia for acute myocardial infarction. In the stepwise analysis of diagnostic and therapeutic issues of acute myocardial infarction one should first of all touch the pre-hospital period.** When speaking of the pre-hospital period in AMI, **the need for transition from symptomatic to pathogenetic treatment should be noted.** It must be confessed that for a long period of time the major objective for an emergency team was the analgesia and fastest possible arrival to the nearest hospital. By no means minimizing the importance of these issues, we think, that along with these measures pathogenetic therapy must be initiated already at the pre-hospital stage. **In AMI this therapy must be aimed at preservation of ischemic, but still viable myocardium of the peri-infarction area. This area can remain viable for hours and even days, thus allowing for successful reperfusion procedures both at pre-hospital stage and during hospital stay.** Above all this implies measures to restore the impaired coronary circulation, that is, the thrombolysis and its role in the early management of AMI. For several decades thrombolysis, both systemic and intracoronary, has been known to provide at least partial restoration of the blood-flow in the infarct-related artery (IRA), thus improving the prognosis and functional capability of the left ventricle owing to preserved viability of the peri-infarction myocardium. At the same time, thrombolysis procedure is not a standard in Russia and is used occasionally. **For example, the rate of thrombolysis among MI patients in Moscow is ≥12%, this value is even lower in other regions of Russia.** The vast majority of therapeutic procedures are performed after patient's admission to hospital, i.e. with a delay between the onset of chest pain and the onset of management. Meanwhile, it is well known, that the sooner is the onset of thrombolysis, the higher is the probability of vessel opening and improvement of both early and long-term prognosis. **Therefore, a question arises concerning the need for thrombolysis at pre-hospital stage.** Efficacy of these methods was advocated by many authors, who had performed thrombolysis with high rate of success and low rate of complications. This pilot study of pre-hospital systemic thrombolysis was performed in cooperation with Moscow emergency care service





provided an additional evidence of efficacy and safety of IRA reperfusion. Efficacy of thrombolysis has been documented by urgently selective coronary angiography performed immediately after the admission to hospital. The above facts allow us to recommend pre-hospital systemic thrombolysis for routine use in MI patients, excluding those with strict **contraindications**:

1. Uncontrolled bleeding.
2. History of stroke or other severe brain injury.
3. Surgery or severe injury within the last 3 months.
4. Uncontrolled hypertension.
5. Prolonged (over 10 min) resuscitation.
6. Severe coagulation disorders.
7. Prolonged warfarin intake.
8. Treatment with IIB/IIIA receptors blockers within the last week.
9. Pregnancy.

Undoubtedly, systemic thrombolysis must be accompanied by generally adopted measures: allow me not to dwell on them because of the lack of time.

The use of cardiocytoprotective agents is another example of the good prospects of AMI therapy at pre-hospital stage and during hospital stay. Today cardiologists are armed with quite effective cardiocytoprotectors, which can be used to prevent myocardial death both after reperfusion and during ischemia of peri-infarction and infarction areas. **For the last two years we have been earnestly engaged in this problem, which has lead us to studies with intracoronary infusion of these agents in AMI patients. As no one has ever performed such studies, we have registered them as our invention. This study has provided strong evidence, that intracoronary infusion of cardiocytoprotectors (Mexicor or Neoton) simultaneously with reperfusion of IRA contributes to preservation of viable peri-infarction myocardium, thus maintaining left ventricular function at the higher level compared to patients without cardiocyte protective therapy.**

This is confirmed by the fact, that blood level of cardiospecific enzymes in patients receiving cardiocytoprotectors was significantly lower as compared to patients without such treatment. At the same time, baseline level of serum enzymes, i.e. prior to cardiocytoprotective therapy, was similar in the study groups.

The fact, that patients, who had received intracoronary cardiocytoprotectors, had significantly higher left ventricular ejection fraction after therapy as compared to patients without such therapy, whereas baseline LVEF values in the study groups were similar, serves as another evidence of the above. Our results suggest, that cytoprotectors contribute to preservation of viable ischemic cardiomyocytes after reperfusion in AMI patients. **Consequently, this offers an opportunity of extensive use of cardiocytoprotectors, both intracoronary (immediately after IRA recanalization) and, more importantly, intravenously at**

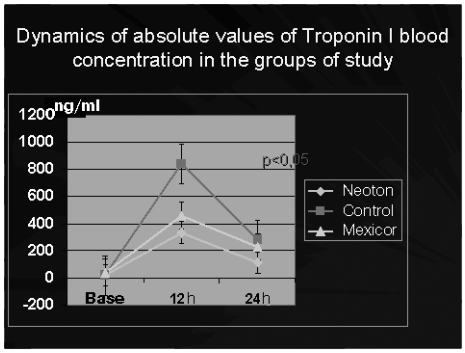


Figure 2.

pre-hospital stage, immediately after systemic thrombolysis. Intravenous use of cardiocytoprotectors at pre-hospital stage in AMI patients is, to our belief, reasonable even without thrombolysis, i.e. without any signs of myocardial reperfusion, as the drug can penetrate left ventricular peri-infarction area through the existing intersystem and intrasystem coronary anastomoses.

Another question to be analyzed separately is the urgent selective coronary angiography and left ventriculography, as well as those endovascular therapeutic methods that follow. This pertains to patients with Q-wave MI, including those after pre-hospital systemic thrombolysis, as the latter not necessarily provides IRA reperfusion; but even with successful thrombolysis recanalization leaves the so-called residual stenosis in the majority of cases, which substantially impairs local coronary flow, especially since reocclusion during hospital stage is known to occur in 22% of cases leading to recurrent AMI in 10-12% of cases. This became especially reasonable after clinical implication of coronary stenting. **Therefore, systemic thrombolysis should be regarded as the first stage of IRA reperfusion, allowing for early partial antegrade reperfusion of IRA, however, more complete and prolonged reperfusion of IRA requires selective coronary angiography and left ventriculography (followed by IRA angioplasty** or angioplasty of other coronary arteries when indicated) to be performed on the next stage as soon as possible. As stated above, these procedures should be performed as soon as possible. **Therefore, systemic thrombolysis and PTCA of the IRA should be regarded as complementary methods on various stages of treatment, rather than alternative methods.**

In this connection, the choice of hospital to which the patients with Q-wave AMI should be admitted is particularly important. Speaking of Moscow, I can unambiguously say, that there's an number of hospitals with interventional radiology departments enough to perform urgent or semi-urgent endovascular therapy in patients with AMI. The same applies to many large cities of Russia. Thus, certain administrative measures and financial support can set up urgent endovascular care for AMI patients in many regions.

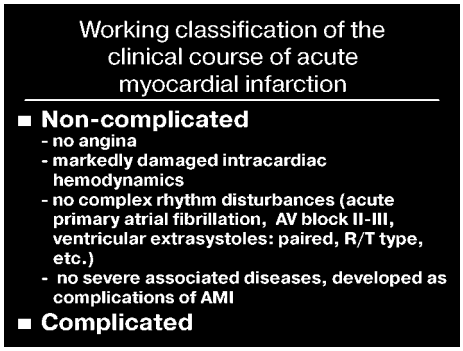
The hard core of the above mentioned facts is that patients with Q-wave AMI should be admitted

to hospitals with round-the-clock (so-called NON-STOP) interventional radiology service instead of other hospitals, unless such service is unavailable.

Thus, after admission to hospital, diagnostic and therapeutic procedures that follow should be accompanied by urgent selective coronary angiography and left ventriculography in Q-wave AMI patients within the first 6 hours after AMI (or later if chest pain episodes persist). Depending on the results, endovascular therapy or, when such are contraindicated, extended medical therapy should be performed. **Worthy of notice is the fact, that IRA reperfusion should be accompanied by intracoronary administration of cardiocytoprotectors. I also wish to say, that endovascular reperfusion of IRA should be aimed at correction of impaired perfusion in other coronary arteries as well, i.e. the complete myocardial revascularization. In cases when a patient is beyond the first 6 hours threshold and there's no chest pain, one should decline urgent selective coronary angiography and adhere to conservative therapy.**

Later on, depending on the clinical course, which can be uneventful or complicated, diagnostic and therapeutic strategy can slightly vary. (slide) What must be remembered is that there's a minimum standard of studies, without which the patient can not be discharged from the hospital.

If the clinical course is uneventful, at day 2the



patient should be transferred from ICU to the department of emergency Cardiology, administered ambulant regimen and oral medications. The mandatory condition is 24-hour ECG monitoring and a stress test performed during hospital stay (8 to 10 days). On the basis of combined data the treatment strategy is defined individually. Absence of transient myocardial ischemia or other alarming signs during 24-hour ECG monitoring, presence of high exercise tolerance and negative stress-test indicate, that the patient should be reallocated to rehabilitation department or cardiological health resort institution after 12 days. The patient should also be clearly advised to receive specialized medical consultation in the event of angina or its equivalent signs in a view of in-hospital examination, including selective coronary angiography with everything that might follow. If during hospital stay a patient develops transient myocardial ischemia on Holter monitors study or has decreased exercise tolerance, as well as positive stress-test, selective coronary angiography and left ventriculography followed by endovascular therapy, direct myocardial revascularization or continued drug therapy (when indicated) should be performed without discharge.

If complications arise, including early postinfarction angina or other equivalents of transient or permanent myocardial ischemia during hospital stay, particularly when in ICU, patients should undergo endovascular procedure, direct myocardial revascularization or continue medical therapy.

This was the brief description of diagnostic and therapeutic measures at pre-hospital and during hospital stay in patients with Q-wave myocardial infarction.

Drug Therapy of Acute Myocardial Infarction

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Recently, it is a common practice worldwide to use the guidelines for treatment of various diseases, including different forms of acute coronary insufficiency. These guidelines are created collectively by prominent specialists in their fields, and following the guidelines provides an adequate level of outcomes. One example: American scientists have analyzed the situation in the U.S.A. hospitals and compared the hospital mortality rate in patients with acute myocardial infarction (AMI) in the in-patient institutions that are following the current guidelines with those that are not strictly following the guidelines. In those institutions that were using the guidelines the mortality rate was virtually 2-fold lower. Let me remind you that I was referring to the U.S.A. Now lets talk about our country. Unfortunately, for a long time we followed the common idea that we are, if not the best, at least no way inferior to the leading countries, particularly in the field of cardiology. However, objective appraisal shows that this is not quite that way. In 2002, Russia participated in a large international trial, and the analysis demonstrated that we were far from the best there .

The reason for that seems to be less common use of so-called hi-tech methods for treatment of AMI, as professor David Iosseliani has mentioned already. Today in my speech about the drug therapy for AMI the matter of discussion is the basic treatment of AMI assuming it has no complications, which is based on the most current international guidelines.

What comprises the modern medical therapy of patients with AMI? First and foremost, it includes analgesia, prevention of ventricular fibrillation, nitrates, antiaggregants, anticoagulants, restoration of the coronary blood flow, both drug-based and non-drug-based, beta-blockers, ADP inhibitors, and, since recently, statins.

There was nothing essentially new in analgesia for the last 30 years; we still use morphine sulfate to relieve pain as we did before. At least that's true for the vast majority of the cardiologists. There surely are significant changes in the aspect of ventricular fibrillation prevention, and they lie, before all, in stopping of preventive treatment with lidocaine. Now the basis of the ventricular fibrillation prevention consists of two things: adequate application of beta-blockers and restoring the normal electrolyte balance. This is most applicable to the serum potassium level.

There is one relatively new moment that appeared in the last year. You know that for many years, since the early 60-s to be exact, after the famous works of Polaris, we returned more than once to the issue of efficiency or inefficiency of the so-called "polarizing solution" (glucose-potassium-insulin solution). By now, this issue is closed. This solution has no effect whatsoever. Last year there was a report of a large study, which included over 20,000 patients. In this study the drugs comprising the "polarizing solution" were used in very high concentrations. Suffice it to say that insulin was administered in over 50 units per 24 hours, and there was a substantial dosage of potassium chloride used, and also there was a high volume load — 2,500 ml per 24 hours. The result of these was null.

A group of Dutch researchers reported the results

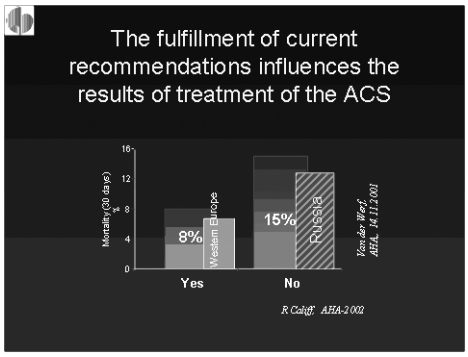

Figure 1.

of application of potassium-glucose-insulin solution in patients all of which underwent primary coronary angioplasty. The results were null as well. Therefore, as of today, we may exclude the potassium-glucose-insulin solution from our everyday practice.

The role of nitrates is certainly important. I'm not going to talk about the theoretical rationale details of usage of these drugs herein, but I will start from demonstrating the experimental studies which show that administration of nitrates in a timely manner — in this case, the infusion of nitroglycerine is meant (I must emphasize, in experimental conditions), — substantially reduces the extent of ischemic damage to the myocardium. These data have later been supported by clinical trials. To be completely honest, I personally don't have a total certainty that nitrates in uncomplicated Q-wave MI produce such a substantial reduction of mortality. But, as to my opinion, there certainly is a benefit in using those.

I'll give one practical detail, which concerns any drug that actually works. Such drug will demonstrate its maximum of efficiency in the most severely ill patients with the worst prognosis. That concerns not

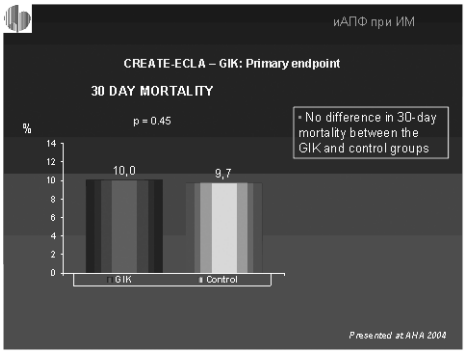

Figure 2.

only the nitrates, but also ACE inhibitors etc.

I'd like to point out the results of the study conducted by our German colleagues. It involved the patients who concurrently received thrombolytic therapy and isosorbide dinitrate. In those cases when the restoration of the coronary blood flow was achieved, the extra effect of nitrates was nearly undetectable. At the same time, in those cases where the coronary blood flow could not be restored by thrombolysis, and, as you know, such patients had a far poorer prognosis, the administration of nitrates did produce the effect.

Treatment with antiaggregants is another outstanding chapter in the therapy of MI patients. The no. 1 drug here is aspirin I will allow myself to remind you this scheme: aspirin inhibits the platelet cyclooxygenase, thus breaking the chain of formation of thromboxane A2, which is a potent pro-aggregant, from the arachidonic [NS1]acid. This is the biochemical background of aspirin action. Aspirin significantly reduces the levels of 11-dehydro-thromboxane B2 not only in the conventional dosage of 150, 160, 200 mg, but also in a much lower dosage — 75 mg per day.

It is my opinion that one of the most outstanding studies in the field of cardiology through all of the years for which such studies are being conducted, is the OASIS2 study. It was this study that actually proved the clinical efficacy of aspirin administration. Fascinatingly, such undoubtedly pathogenesis-grounded and potent intervention as restoration of coronary blood flow by thrombolysis actually yields the same actual reduction of mortality as does aspirin alone. It is no doubt an outstanding drug. Let me just remind you that it only costs 9 dollars to save one human life by using aspirin, while it does cost, say, tens of thousands of dollars to save one human life with coronary artery bypass graft surgery. Now imagine that health care authorities have limited funds, what should they spend them for? For providing the whole population of their country with a cheap drug for no charge, or to provide a couple of CABG surgeries?

As for the dosage. Average maintaining dose for aspirin is 75–300 mg/day. I only want to draw your attention to one thing, which needs to be held sacred: the first dose for a previously untreated patient should be no less than 300 mg. If you use what we call the maintaining dose (75 mg/day) initially, then the thromboxane B2 plasma level will reach the target value only at the 2nd, or even, to be precise, at the 3rd day. For acute MI, these timings of drug action are unacceptable. While if you do give the drug in its full dosage, you're going to reach the effect virtually in 30 minutes.

I would like to remind you that cyclooxygenase pathway is not the only way of platelet activation, and there also are some other inductors, particularly ADP. Today we do have potent drugs which affect the ADP-induced aggregation. These include the group of thienopyridine derivatives, particularly ticlopidine. As of today, the most well known drug is clopidogrel. Aspirin and clopidogrel combination appeared to be extremely effective. A study called "CLARITY-TIMI 28" has been completed relatively recently. Patients in this study received a complete course of treatment including thrombolysis, but some of them were additionally given clopidogrel (loading dose and then maintaining dose), while others were not given any clopidogrel. By the end of the first month a substantial difference in results has been shown. When evaluating the outcomes by such parameters as cardiovascular death, recurrent MI and the need for emergency revascularization, the difference between groups was 20%. Clopidogrel does not increase the number of bleeding events. Yet the most interesting data were reported by our Chinese colleagues. They conducted a study in which clopidogrel was given not only to those patients who underwent restoration of coronary blood flow, but generally, to all the patients with MI, not even giving any stress testing. They also demonstrated a significant decrease in the undesirable outcomes. Thus, as of today, clopidogrel is evidently a necessary addition, an essential component of the therapy, which we, from my perspective, may start using even at the pre-hospital stage, if, of course, the patient has no contraindications, although this is not yet in the official guidelines. If such patient is admitted to a center where he may undergo PTA (percutaneous transluminal angioplasty) he will get better preparation for this procedure. If not, anyway, the benefit of administration of such combination therapy is obvious.

Anticoagulants. For some reason we still have a strong belief that MI must be treated with heparin. Actually, no one has proved it. And today in case of the uncomplicated MI — may I remind we are discussing the MI with ST elevation (STEMI) — you are not obligated to treat it with heparin, unless you are a supporter of this method. However, heparin should be used in several special occasions, and there is no doubt that it must be used with some types of thrombolytic therapy. So-called fibrin-non-specific thrombolytic agents, such as streptokinase, which we, unfortunately, are using most often, do not require concurrent heparin administration, while fibrin-specific agents seem to show better results with background heparin. However, why would I remark this point? Well, it's only because we do use heparin in these patients in a wrong way. Today the maximum allowed bolus dose for intravenous administration is 4,000

units. And it would be even more appropriate to calculate the individual dosage, which is 60 units per 1 kg of patient's body weight. Still, no matter how big is the body weight, the initial dose should not exceed 4,000 units. And after that, a maintaining infusion should be continued with the rate of infusion 12 units/kg/hour, however, this still must not exceed 1,000 units per hour if patient weights over 70 kg. If the weight is lower, that is another issue. This is to be controlled by activated partial thromboplastin time (APTT), which should be 1,5–2 times the normal value. Duration of infusion is to be 48 hours, no longer. That is for so-called unfractionated heparin. However, also relatively recently, and also in the developing countries, there was a study of a version of low molecular weight heparin, which I had never heard of before — neither in books, and nor in any other country. It was called rerifarin. This study showed that addition of the low molecular weight heparin may potentially improve the outcomes for patients with any STEMI. Evidently, we cannot use these data in our country because we just don't have that drug here. However, these results do come under notice, and we must be ready to include the low molecular weight heparin into the list of drugs recommended for the treatment of such patients once we obtain the appropriate evidence.

Now there are the latest data, literally three days old. These are the results of the EXTRACT-TIMI 25 study. This study, in which Russia participated as well (and we did recruit the biggest number of patients in it), compared the results of treatment with enoxaparin vs. unfractionated heparin in patients with acute MI receiving thrombolytic therapy. The study showed that enoxaparin was much more effective than unfractionated heparin. I'm not going into details of this study, but I want to draw your attention to the fact that the low molecular weight heparin is associated with bleeding complications significantly more often.

There is another issue I'd like to cover. You are aware that there are different classes of polysaccharides that have anticoagulant properties. If the number of sugar units is large, about fifty, that is unfractionated heparin. If there are about 18 units, that is a low molecular weight heparin. And, lastly, a relatively new class of anticoagulants has recently been introduced. This one consists of a small number of sugar units and selectively affects the factor Xa. When the unfractionated heparin is used, it affects the factor II; low molecular weight heparin has nearly equal effect on the factors II and X; and administration of pentasaccharides produces influence only on the factor Xa. Several days ago the results of a new study, OASIS 6, have been reported. This study has quite a complex design. I don't have an opportunity to go into details with it now, but, in essence, it compared the effectiveness of fondaparinux and unfractionated heparin in various treatment options of acute MI patients, including thrombolysis, primary angioplasty, and in patients who had not received any of the methods of coronary blood flow restoration. I will only mention one result of comparing fondaparinux with unfractionated heparin in patients who had their coronary blood flow restored with thrombolytics. Fondaparinux has substantial advantages over the unfractionated heparin. And, if we are to recall the results of another study, OASIS 5, in which attention was focused on the acute coronary syndrome without ST elevation, and has compared the fondaparinux with the low molecular weight heparin, fondaparinux there also showed its undoubted benefits, therefore we may conclude that quite soon we will have a sufficiently effective anticoagulant being significantly less expensive than low molecular weight heparin.

Beta blockers. I'm not reminding their mechanism of action. Their use in acute MI is surely positive. I'll present the results of one German study performed in the North Rhine-Westphalia Land, which I like very much. Clinical studies may have various structures. One option is to have a specially constructed design with strict eligibility criteria etc. Such studies have their benefits, and we couldn't make it without them today, but they also have their significant limitations. Yet there is another kind of analysis, the one which our German colleagues employed. They took all the patients undergoing treatment in this region of Germany with the diagnosis of "myocardial infarction". They didn't pay attention to its details, such as whether it has complications or not, whether there is concurrent diabetes mellitus or there isn't, they just included everyone, who had the diagnosis of myocardial infarction. And then they evaluated the results and outcomes in those patients who received beta blockers and in those who did not. It appeared that the hospital mortality rate in those who received beta blockers was 8%, while in those, who did not receive these agents, the rate was virtually 2-fold higher. Today I also would like to state specially that the first dose of beta-blockers should apparently be administered intravenously. I have already mentioned more than once that the myocardial infarction is a rather dynamical process, that is why we are very anxious to have the result neither somewhat later, nor tomorrow, but today, and not in an hour, but it better be in the next few minutes. Now consider that if you start treating the patient with the oral tablets of beta-blockers, you'll achieve the appropriate decrease of heart rate (and this is usually the sign that we judge the adequacy of the dosage by) only within somewhere 1,5 days. This time interval is absolutely unacceptable in case of MI. While when we start the intravenous administration of the drug, we get the appropriate result literally in several minutes.

Angiotensin-converting enzyme inhibitors. Myocardial infarction involves remodeling of the left ventricle, and the angiotensin-converting enzyme inhibitors prevent this process from developing, by which they significantly improve the outcomes for patients, especially for those who have their left ventricle function compromised. Use of ACE inhibitors helps saving 57 lives per every thousand of treated

patients. It is especially interesting that this is achieved not only by reducing the number of people with progression of the heart failure, but also by decreasing the occurrence of the recurrent MI.

There are some issues regarding ACE inhibitors that I would like to shed some light upon today.

First. I must say that one of the founders of this trend, Dr. Pfeffer, was in his time advocating to start the ACE inhibitors therapy not immediately, but 10-14 days after MI onset. His opinion was based on his ideas about the development of the remodeling processes etc. This might have had some background, theoretically. And it was for a long time that there was a common concept to use the ACE inhibitors accurately in these timing terms. However, when the results of the actual studies were analyzed, it appeared that if the total number of people with MI saved thanks to ACE inhibitors was 100%, then the 40% of these 100 were saved in the first 24 hours, i.e. in the cases of an early start of ACE inhibitors administration. If we look at the first week, that will be another 43%. Therefore, ACE inhibitors must be started as soon as possible, right after the stabilization of hemodynamics, or, to speak in simple terms, when the systolic blood pressure is higher than 100 mmHg.

The second issue which has been under discussion for a long time, and, for some reason, especially long in our country: can ACE inhibitors be given concurrently with aspirin? Administration of aspirin to such patients is out of question, as we know. But, supposedly, ACE inhibitors and aspirin are the combination that eliminates the effects of both drugs. Currently, it has been shown to be wrong assumption, and in any case the ACE inhibitors may be given concurrently with aspirin, without any impact to the effectiveness of either agent. All that I'm talking about is not only our personal data, this is the evidence obtained in large international studies.

The contraindications for ACE inhibitors are common knowledge.

And, finally, the last thing I would like to talk about today, is the use of statins. Similarly, statins were considered to be the agents for administration in later terms of the acute myocardial infarction, but life gave some amendments to the issue. Swedish researchers studied the long-term treatment outcomes in two groups of patients with MI: The 1-st group started receiving the statins during hospitalization, while the 2-nd group started statins later, after being discharged from hospital. It appeared that by the end of one year there was a significant difference in prognosis between the two groups. After that special studies were initiated which were evaluating exactly this issue, and they, evidently, showed that early administration of statins is quite reasonable. Generally, I must point out, that these drugs are just amazing, and their mechanism of action is sometimes not very clear. Recently, I've read an article in which there is an analysis of outcomes for patients who have experienced MI and suffer from ventricular tachycardia. Obviously, people without ventricular tachycardia must have better prognosis than those who do have the ventricular tachycardia. But, if both of these groups are receiving statins, their prognosis becomes virtually similar. The mechanism for that is unclear, but the fact is supported by evidence. Importantly, the statins should be used in all patients with MI, regardless of their lipid profile. If you look at the patients who have their baseline level of cholesterol and low density lipoproteins above 130, which is the group of those who, seemingly, are most demanding such therapy, in this group you get the undoubtedly positive result. If you look at those patients who have their level of cholesterol and low density lipoproteins within the range of 100 to 120 mg — you'll see the same result. But most fascinatingly: if you look at the patients who have their level of cholesterol and low density lipoproteins below the level just recently considered to be the target level, statins produce the same result, no different from the first and the second groups. Therefore, statins, in the absence of any serious contraindications, should be given to all of the patients with acute MI, at any stages of the process and, naturally, in the late terms too.

What I have just listed is the basis of the drug therapy of patients with acute MI. Following these approaches plus, naturally, restoration of coronary blood flow, allowed for a significant decrease of the hospital mortality rate, which, however, did not reach the figures mentioned here by David Iosseliani; we have 4,5% mortality rate for the large-focal MI, but, nevertheless, it is substantially lower than it was 60 years ago, when it amounted to about 30-40%.

Primary Percutaneous Coronary Intervention (PCI) for ST-Segment Elevation Myocardial Infarction (STEMI). Results of a German University Hospital

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Introduction

Acute myocardial infarction is caused by plaque rupture with subsequent vessel occlusion. In the case of early reperfusion myocardial necrosis can be avoided or limited. Numerous randomized trials have demonstrated that percutaneous coronary intervention (PCI) is superior to intravenous trombolysis with respect to major cardiac and cerebral adverse events (1-3). A recent paper by Zahn and co-workers (4) showed that independent predictors of in-hospital mortality are cardiogenic shock, technical success, age, three vessel disease anterior infarction and volume of primary angioplasty at the hospital. The data were derived from a large prospective registry of the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausarzte (ALKK). Data of unselected patients with STEMI admitted to German university hospitals, however, are missing because university hospitals in Germany are usually not participating in the ALKK registry. Thus, we thought to retrospectively analyze our results of primary PCI at the University Hospital Erlangen over the last six years.

Material and Methods

Data were collected retrospectively from the year 1999 until 2004 and analyzed locally. STEMI was defined as persistent angina pectoris and ST-segment elevation of > 1 mm in at least two standard leads or > 2 mm in at least two contiguous precordial leads. Pre-hospital delay was defined as the time from onset of symptoms until admission to the hospital. In-hospital delay was defined as the time from admission until arterial puncture. Angioplasty was performed according to good medical practice. Success was defined as achieving TIMI flow grade 3. All patients with onset of angina pectoris < 24 hours were analyzed. Patients transferred from another hospital were also included in the analysis.

Patient population is given in absolute numbers, percentages, and mean (SD). Categorical values were compared using chi-square test. or Fisher`s exact test. For all analyses, a two sided p value of <0.05 was considered statistically significant.

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Results

A total of 405 consecutive patients with STEMI were enrolled in the analysis. Ninety patients (n=90) were ≥75 years of age and 28% of patients were female. The majority of patients had arterial hypertension, diabetes mellitus and were smokers. Table 1 gives the demographics of the study population.

Table 1. Demographics (n=405).

Age	68±12	
Female	114	28.1%
Hypertension	283	69%
Diabetes	125	30.9%
Smokers	231	57%
Hypercholesteremia	165	40.7%
Previous MI / PCI	70	17.3%
Previous stroke	36	9%

MI = myocardial infarction. PCI = percutaneous coronary intervention

Anterior infarction was very frequent (185/405; 45.7%) The percentage of patients who had been resuscitated or presented with cardiogenic shock (Killip class IV) was 12.8% (n=52) The number of patients showing an ejection fraction of J25% documented by echocardiography on arrival to hospital was found in 34(8.4%) patients. Onset of angina pectoris to arrival at hospital was 240+251 min, and, hospital-specific PCI related delay was 66+47 min. (Table 2).

Table 2. Baseline characteristics (n=405).

Killip IV	52	12.8%
Anterior infarction	165	40.7%
Ejection fraction < 25%	34	8.4%
Onset of angina	240±251	
Door to angiography	66±47	

In most patients (81%) angiography was started within 90 minutes (Fig 1).

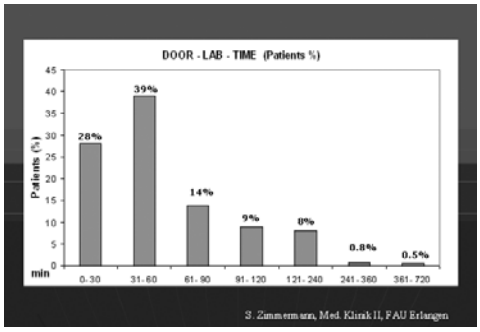

Figure 1.

The left anterior descending artery was the infarct related artery in nearly half of the patients (Table 3).

Table 3. Infarct related artery (n=405).

LMA	9	2.3%
LAD	173	42.7%
CX	44	10.9%
RCA	182	44.9%
SVG	6	1.5%
MVD	174	43.2%

LMA = Left main. LAD = Left anterior descendens. CX = Circumflex. RCA = Right coronary artery. SVG = Saphenous vain graft. MVD = Multivessel disease

Table 4 summarizes the data on the procedure.

Table 4. Procedural data (n=405).

PCI	368*	91%
Stent	330	81.4%
TIMI III	312	77%
GP IIb/IIIa	306	75.6%
Emergency bypass	10	2.5%
Conservative treatment	27	6%

All 405 patients had emergency angiography followed by PCI in 368 (91%) of patients, 89.6% of these received a coronary stent and TIMI flow grade 3 was achieved in 85% (77% of our study population; n=312). IIb/IIIa receptor antagonist were frequently used (n=306; 75.6%). Only medical treatment was performed in 6% of patients (n=27). Thrombolysis was not performed in any patient. Out of the 405 patients 28 patients (6.9%) did not survive hospital stay. In the PCI group (n=368) in-hospital mortality was 5.4% (n=20). Disabling strokes where rare (n=3) (Table 5).

Table 5. In-Hospital outcome (n=405).
(a) = retroperitoneal. (b) = 1 retroperitoneal

Death (all)	28	6.9%
Death (PCI)	20	5.4%
Re-infarction (PCI)	19	5.2%
Stroke (disabling)	3	0.7%
Major bleedings transradial (a)	1	0.6%
Major bleedings transfemoral (b)	2	0.8%
Mean hospital stay	14±9	

Discussion

Outcomes of acute intervention in ST segment elevation infarct (STEMI) in Germany and other European countries have been analyzed in the context of study protocols, but most of these data have been collected in the nineties (4-8, 14) and “real-life” results comprising all consecutive patients including very old patients and late admissions have been less well characterized. We present the current results of a German university hospital from 1999-2004.

In our population overall in-hospital mortality was 6.9% and was only 4.1% after exclusion of patients who had been resuscitated before admission. These data represent the improvement in the management of patients with myocardial infarction over the last decade characterized by early diagnosis and acute treatment as well as by improved mechanical therapies and management of complications (8-11). Former studies showed that the time from the onset of symptoms to treatment is of prognostic importance (12-14). The door to angiography time (as a part of the time to treatment) observed in our analysis is short with a median of 50 minutes (quartiles of 30-75 minutes) and our data are very close to the data of the ALKK registry which had been obtained at 80 German hospitals (4). So our findings confirm very short in-hospital delays for Germany as found in other European registries (14). In comparison with former studies (1, 2, 14) our data show that patients with STEMI undergoing a PCI nowadays more often receive a coronary stent with a successful reperfusion in 85% (TIMI 3). Severe bleeding or stroke were very rare complications in our study population, even if very old patients were included.

Conclusions

Our results indicate that contemporary, stent-based primary intervention in acute ST elevation infarction accompanied by aggressive anticoagulant and antiaggregatory therapy is a safe and successful therapy leading to low mortality and morbidity, even if “all comers”, including very old patients and late admissions, are included.

References

1. Weaver W.D., Simes R.J., Betriu A. et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. JAMA, 1997, 278(23), 2093-8

2. Keeley E.C., Boura J.A., Grines C.L. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet, 2003, 361(9351), 13-20

3. Widimsky P., Budesinsky T., Vorac D. et al. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial—PRAGUE-2. Eur. Heart J., 2003, 24(1), 94-104

4. Zahn R., Vogt A., Zeymer U. et al. In-hospital time to treatment of patients with acute ST elevation myocardial infarction treated with primary angioplasty: determinants and outcome. Results from the registry of percutaneous coronary interventions in acute myocardial infarction of the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausarzte. Heart, 2005, 91(8), 1041-6

5. Heer T., Schiele R., Schneider S. et al. Gender differences in acute myocardial infarction in the era of reperfusion (the MITRA registry). Am.J. Cardiol., 2002, 89(5), 511-7

6. Zahn R., Schiele R., Schneider S. et al. Clinical practice of primary angioplasty for the treatment of acute myocardial infarction in Germany: results from the MITRA and MIR registries. Z. Kardiol., 2002, 91, Suppl. 3, 64-71

7. Andersen H.R. et al. and DANAMI-2 Investigators. Danish multicenter randomized study on fibrinolytic therapy versus acute coronary angioplasty in acute myocardial infarction: rationale and design of the danish trial in acute myocardial infarction-2 (DANAMI-2). Amer. Heart J., 2003, 146, 2, 234-241
8. Zijlstra F., Hoorntje J.C., de Boer M.J. et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N. Engl. J. Med., 1999, 341(19), 1413-9
9. Ryan T.J., Antman E.M., Brooks N.H. et al. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary and recommendations: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). Circulation, 1999,100,1016–1030
10. Grines C.L., Browne K.F., Marco J. et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction: the Primary Angioplasty in Myocardial Infarction study group. N. Engl. J. Med., 1993, 328, 673–679
11. Suryapranata H., van't Hof A., Hoorntje J.C.A. et al. Randomized comparison of coronary stenting with balloon angioplasty in selected patients with acute myocardial infarction. Circulation, 1998, 97, 2502–2505
12. Brodie B.R., Stuckey T.D., Wall T.C. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. J. Am. Coll. Cardiol., 1998, 32, 1312–1319
13. van't Hof A.W.J., Liem A.L., Suryapranata H. et al. Clinical presentation and outcome of patients with early, intermediate and late reperfusion therapy by primary coronary angioplasty for acute myocardial infarction. Eur. Heart J., 1998, 19, 118–123
14. De Luca G., Suryapranata H., Zijlstra F., et al. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. J. Am. Coll. Cardiol., 2003, 42(6), 991-7