Improving Balloon Angioplasty: Lessons Learned from the DCB and Stent Trials

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Background

For over 40 years, balloon angioplasty (POBA) has been used to treat vascular disease. Numerous randomized clinical trials (RCTs) confirmed superior outcomes of stents and paclitaxel-coated balloons (DCB) over POBA. Many of these studies, used the same control — POBA. So, if patient/lesion characteristics were similar, it would be reasonable to expect that results for the POBA control groups would be similar in these studies. An analysis was made of RCTs between 1996-2015 with similar endpoints, patient and lesion characteristics (Figs. 1-2).

Results and Discussion

Angiographic and clinical outcomes of DCB and stents were similar, and all were superior to POBA (Figs. 3-4). However, outcomes in the POBA control groups varied by as much as a factor of 4 (Fig. 5). Since standard POBA catheters were used in accordance with the investigators' "standard technique," the variance may be due to differences in POBA technique amongst the various investigators. For example, In the LEVANT 2 and IN.PACT SFA trials, outcomes for the PTA cohort appeared to be better in the hands of US operators than OUS operators (Fig. 6). POBA outcomes were superior when techniques were used employing a gradual step-wise expansion of the vessel, such as pre-dilatation (Fig. 7). Studies of smooth muscle cells showed that injury was a function of strain rate, not the magnitude of the applied stress, as the cell membrane is viscoelastic (Fig. 8). This was demonstrated in vivo, where a slow, gradual inflation to the balloon's nominal pressure resulted in lumen expansion with no vessel injury. But when the same balloon was rapidly inflated to the same nominal pressure, there was extensive dissection and vasoconstriction (Fig. 9). In the PACIFIER trial, the DCB cohort had 2X more pre-dilatation than the PTA cohort, which resulted in a lower dissection rate; whereas in IN.PACT SFA, both arms had the same rate of pre-dilatation, and there was no difference in dissection rate (Fig. 10). In coronary artery studies, a number of investigators showed that slow, gradual, low-pressure inflation protocols often resulted in better acute outcomes (Fig. 11). These techniques also increase the inflation time. In a prospective RCT of short vs long inflation time in infrainguinal PTA, longer inflation times were shown to reduce severity of dissection and need for additional intervention (Fig. 12).

Conclusion

In randomized clinical trials, pay close attention to the control group. "Plain Old Balloon Angioplasty" remains to be a very important tool in the catheter lab, and like most tools, results are related to how they are used. Techniques that employ slow, gradual, low-pressure balloon inflations may help improve outcomes.

DCB vs POBA RCTs

THUNDER	FEMPAC
LEVANT 1	PACIFIER
BIOLUX P-1	DEBELLUM
IN.PACT-SFA	LEVANT 2

Fig. 1

STENT vs POBA RCTs

BENESTENT	STRESS I-II
ISAR-SMART	START
EPISTENT	VIABAHN
ABSOLUTE	FAST
ZILVER PTX	ASTRON
RESILIENT	SUPER

Fig. 2

DCB vs. PTA: 6 Month LLL (mm)

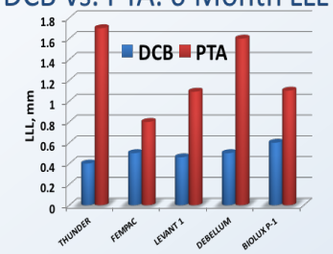


Fig. 3

DCB vs. PTA: 12 Month TLR (%)

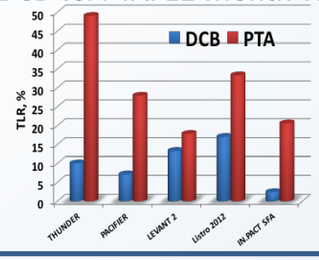


Fig. 4

"Control" PTA in Stent and DCB RCTs

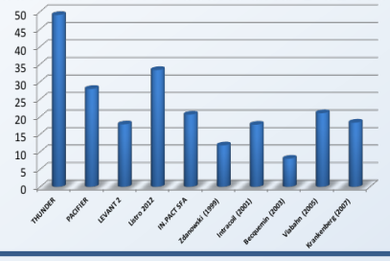


Fig. 5

US vs. OUS Sites — PTA Cohorts

Freedom from TLR at 1 Year

	US	OUS
LEVANT 2*	83.3%	71.7%
IN.PACT SFA**	83.9%	74.5%

*http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM400420.pdf

**G Tepe et al; Circulation. 2015;131:495-510

Fig. 6

"Control" PTA in DCB RCTs

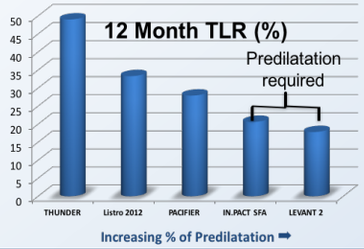


Fig. 7

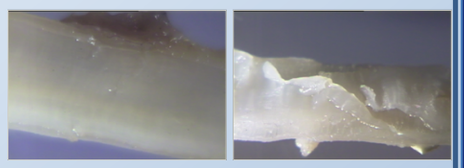
Cellular Injury Model

Vessel injury is related to the *rate* at which the vessel wall is stretched (strain rate)

Barbee, K. & Thibault, L.: Advances in Bioengineering, ASME, pp. 28-31, 1991
Barbee, K., et al: Ann. Biomed. Engr. 22:14-22, 1994

Fig. 8

In Vivo Porcine Study of Balloon Inflation Rate



Slow to 8 atm — Rapid to 8 atm

Fig. 9

Pre-dilatation vs. Dissection

	DCB Dissection	Control PTA Dissection	P-value
PACIFIER*** Pre-dil at op discretion	47.4%	73.5%	0.03
In.PACT SFA** Pre-dilatation	63.8%	61.1%	NS

PACIFIER: DCB cohort had 2X more pre-dilatation than PTA cohort - LOWER DISSECTION IN DCB

IN.PACT SFA: Same pre-dilatation in both arms - NO DIFFERENCE IN DISSECTION RATE

**G Tepe et al; Circulation. 2015;131:495-510
***M Werk et al; Circ Cardiovasc Intervent 2012; 5:831-840

Fig. 10

PTCA Clinical Studies

Gradual, low pressure balloon inflation minimize trauma

R. Solar, T. Ischinger. Cardiovasc Revasc Med, 2003
Schmitz, et. al. Am Heart J., 1996
R. Ilia, et. al. Cath. Cardiovasc. Diag., 1993
F. Shawl. Cath. Cardiovasc. Diag., 1993
P. Chenu, et. al. Cath. Cardiovasc. Diag., 1993
V. Banka, et. al. Am. Heart J., 1993
D. Leibowitz, et al. Cardio Revasc. Medicine, 2009

Fig. 11

Infrainguinal PTA — Short vs Long Inflation

	Inflation Time (sec)		
	30	180	P-Value
Major dissection (grades 3 or 4)	43%	14%	.009
Minor or no dissection (grades 1 and 2)	57%	86%	.009
Further interventions (Stent, repeat dilatation, dilation with larger diameter)	54%	28%	.017
Residual stenosis (>30%)	32%	14%	.096
Complication (embolization, thrombosis)	1	1	-
Mean ankle-brachial index (before, after intervention)	0.66, 0.87	0.65, 0.84	

N. Zorger et al. J Vasc Interv Radiol. 2002

Fig. 12