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Meta-analysis of the long term effects of different interventions on chronic total coronary occlusions

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Abstract. – BACKGROUND: Coronary chronic total occlusion (CTO) is the end stage of coronary artery atherosclerosis. CTO revascularization can be performed by percutaneous transluminal coronary angioplasty (PTCA), bare metal stent (BMS) or drug-eluting stent (DES). It is important to scientifically evaluate the effectiveness of CTO interventional treatments.

METHODS: Relevant studies of long term outcomes for several kinds of CTO treatments were examined. Data were extracted and assessed by two independent clinical experts, pooled and analyzed using meta-analysis.

RESULTS: (1) Totally 8 articles comparing outcomes between PTCA and BMS treatment were analyzed. Follow-up variables such as mortality, subsequent coronary artery bypass graft surgery (CABG), re-occlusion, re-stenosis and target lesion revascularization (TLR) were analyzed by meta-analysis. Compared with BMS intervention, PTCA was associated with significant higher rate of re-occlusion, re-stenosis, subsequent PTCA and TLR. (2) Totally 12 articles compared long term outcomes between BMS groups and DES groups, encompassed 3605 CTO patients. During the long-term follow-up, six variables as major adverse cardiac events (MACE), myocardial infarction, all-cause death, subsequent CABG, accumulated MACE-free survival rate, re-stenosis/re-occlusion rate were analyzed by meta-analysis. Compared with patients in DES groups, patients in BMS groups had significant higher MACE, subsequent CABG, re-stenosis/re-occlusion rate, TLR, target vessel revascularization, while lower MACE-free survival rate.

CONCLUSIONS: Incidence of re-occlusion, re-stenosis, subsequent PTCA and TLR were significantly lower for BMS implantation than for PTCA procedure. Variables, including MACE, subsequent CABG, re-stenosis/re-occlusion rate were higher while accumulated MACE-free survival rate was lower in BMS groups than in DES groups.

Key Words:
Coronary artery chronic total occlusion, Percutaneous transluminal coronary angioplasty, Recanalization, Drug-eluting stent, Bare metal stent, Long term follow-up, Meta-analysis, Systematic review.

Introduction

Coronary chronic total occlusion (CTO), involved in one third of the coronary diseases, is the end stage of coronary artery atherosclerosis[1]. CTO can result in myocardiolysis, myocardium ischemia, reduction of the number of myocardial cells and ventricular remodeling which lead to decreased myocardium contractile, leading to a reduction of the quality of life and poor prognosis[2]. Medication treatment alone may only reduce the clinical symptom in CTO patients while has little effect on the long-term heart function and the improvement of the patients' survival rate[3].

CTO revascularization can be performed by percutaneous transluminal coronary angioplasty (PTCA), bare metal stent (BMS) or drug-eluting stent (DES)[4]. PTCA for CTO treatment is reported to be associated with significant residual stenosis and high incidence of re-stenosis[5]. In the last decade, remarkable progress has been attained in the percutaneous treatment of coronary artery disease[6]. Back to the 1990s, the success rate of bare metal stents was 86-88% with a re-stenosis rate of 30%-40%[7]. Over the recent decade, drug-eluting stents have been developed to reduce the high rate of re-stenosis following percutaneous coronary revascularization[8]. It has been reported that, compared to BMS, DES has been shown to remarkably reduce the incidence of both re-stenosis and subsequent revascularization[9]. The advantage of drug-eluting stents has been suggested in CTO patients with specific lesions or acute myocardial infarction[10].

In spite of advanced technologies and improved outcomes after revascularization, CTO remains a source of physiological frustration and clinical uncertainty. Although opportunity to achieve recanalization is growing for chronic total occlusions using DES, these patients are still recognized as a formidable barrier to successful percutaneous revascularization[11], as the long term

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outcomes such as cumulative survival rate, major adverse cardiac events (MACE), incidence of re-stenosis and re-occlusion are still under debate based on different procedures and technologies. Therefore, it is important to scientifically evaluate the effectiveness and influential factors for CTO interventional treatments.

In this study we systematically reviewed publications on the long term outcomes of several treatments in CTO patients and found that revascularization performed by DES implantation is superior to by PTCA or by BMS implantation in reducing the rates of MACE and target lesion revascularization (TLR), as well as the incidence of re-stenosis and re-occlusion.

Methods

Selection Criteria for Articles

Data bases, such as Embase, PubMed, Medline, Ovid, CCTR, CNKI and CMBdisc, were searched by two investigators independently. Additional manual search was also used for related meeting abstracts and websites including American Heart Association, American College of Cardiology, European Society of Cardiology and national postgraduate thesis pool (from January 1990 to December 2009). The key words for searching included "CTO", "PCI", "PTCA", "BNS", "stent" "long-term" "follow-up" and "outcome". There is no language restriction in our selection. The criteria for selected studies comprised: 1, patients with CTO diseases more than two weeks, 2, comparisons of patients under PTCA, DES or BMS treatment, 3, follow-up period of which is at least half a year. Studies with incomplete data or cases number less than 50 were excluded from the analysis.

Data Extraction

Two independent investigators selected clinical publications with pre-specified data forms. Meta−analysis was assessed by two independent clinical experts, pooled and analyzed by fixed-effect model and random-effect model[12].

Quality Assessment

The quality of eligible articles was assessed by two independent investigators according to the Cochrane Handbook with established methods. Five items were included, including randomization, blinding, allocation concealment, comparability and withdrawal of baseline and reported follow-up.

Statistical Analysis

Heterogeneity was assessed using the I^2 test, Q test, L'abbe and Galbraith[13]. An $I2$ value > 50% was considered as heterogeneity. If no statistical heterogeneity was found, continuous variables and dichotomous were compared using a model for fixed effects. Searching Software for analysis were Comprehensive Meta Analysis 2.0 and Metanalysis 1.0.

Results

Publications included in our study are between 1990 and 2009. We used a fixed-effects model to analyze heterogeneity statistically among studies. Two different aspects were studied, comparison of long term outcomes between PTCA and stent implantation, and comparison of long term outcomes between drug-eluting stents and bare metal stents.

Study of the Long Term Outcomes Between PTCA and Stent Implantation on CTO Recanalization

Totally 8 articles compared long term outcomes between PTCA and BMS groups, encompassed 2865 CTO patients (Table I). Six follow up variables (followed up for more than six months) as mortality, subsequent coronary artery bypass graft (CABG), re-occlusion rate, re-stenosis rate, subsequent PCI and target lesion revascularization (TLR) were analyzed by meta-analysis. Compared with BMS intervention, PTCA was associated with significant higher rate of re-occlusion (OR, 3.478, 95% CI, 1.966-6.153, $p <$ 0.001, heterogeneity, Q = 3.281 p = 0. 512I^2 = 0.00%) (Figure 1), re-stenosis (OR, 028, 95% CI, 1.354-6.774, p = 0.007, heterogeneity, Q = 19.849, p = 0.00, I^2 = 79.847%) (Figure 2), subsequent PTCA(OR, 3.017, 95% CI, 1.957-4.653, $p < 0.001$, heterogeneity, Q = 1.081, p = 0.897, I^2 = 0.00%) (Figure 3), TLR (OR, 2.57, 95% CI, 1.762-3.748, $p < 0.001$, heterogeneity, Q = 1.707, p = 0.635 I^2 = 0.00%) (Figure 4). The other factors, including all cause death (OR, 2.179, 95% CI, 0.464~10.235, p = 0.324, heterogeneity, Q = 0.436, p = 0.933, I^2 = 0.00%) and subsequent CABG (OR, 1.272, 95% CI, 0.581-2.748, p = 0.548, heterogeneity, Q = 3.446 p = 0.629 I^2 = 0.00%), did not show significant difference between PTCA groups and BMS groups.

Study of the Long Term Outcomes Between Drug Eluting Stents and Bare Metal Stents on CTO Recanalization

Totally 12 articles compared long term outcomes between BMS groups and DES groups (Table II),

Table I. Characteristics of seven included studies.

Study	Year of publication	No. of patients	Experiment protocol	Country	Occlusion time	Clinical follow-up (month)
Rahel et al.[19]	2004	200	Random control	Netherlands	>2 weeks	12
Rubartelli et al.[20]	1998	97	Random control	Italy	>4 weeks	9
Simes et al.[21]	1996	113	Random control	Norway	>2 weeks	6
Hoher et al.[22]	1999	80	Random control	Germay	>4 weeks	6
Tamai et al.[23]	2004	217	Random control	Netherlands	>2 weeks	6
Dong et al.[24]	2000	85	Parallel control	China	>4 weeks	6
Ozaki et al.[25]	1996	269	Parallel control	Nehterlands	>12 weeks	6

Model	Study name	Subgroup within study	Statistics for each study					Odds ratio and 95% CI
			Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01 0.10 1.00 10.00 100.00
	Rubartelli	9m	5.935	1.812	19.443	2.942	0.003	
	Tamai	6m	4.700	0.988	22.349	1.945	0.052	
	Simes	6m	2.500	0.931	6.710	1.819	0.069	
	hoher	6m	10.560	1.239	90.008	2.156	0.031	
	Dongshaoh	6m	1.959	0.597	6.428	1.109	0.267	
Fixed			3.478	1.966	6.153	4.283	0.000	
Random			3.478	1.966	6.153	4.283	0.000	

Figure 1. Pooled results of re-occlusion rate of patients in PTCA groups and BMS groups.

encompassed 3605 CTO patients. During the long-term follow up, variables such as MACE, myocardial infarction (MI), all-cause death, subsequent CABG, accumulated MACE-free survival rate, re-stenosis/re-occlusion rate, TLR and target vessel revascularization (TVR) were analyzed by meta-analysis. Compared with patients in DES groups, patients in BMS groups had significant higher MACE (OR, 3.513, 95% CI, 2.297-5.374, $p < 0.001$, heterogeneity, Q = 34.369, $p < 0.001$ $I^2 = 70.904\%$) (Figure 5), subsequent CABG (OR, 4.614, 95% CI, 1.498-14.219, $p = 0.008$, heterogeneity, Q = 2.085, $p = 0.555$, $I^2 = 0.00\%$) (Figure 6), re-stenosis/re-occlusion rate (OR, 11.825, 95%

Model	Study name	Subgroup within study	Statistics for each study					Odds ratio and 95% CI
			Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01 0.10 1.00 10.00 100.00
	Tamai	6m	0.895	0.508	1.575	-0.386	0.699	
	Simes	6m	5.911	2.620	13.337	4.280	0.000	
	Rubartelli	9m	4.533	1.930	10.648	3.469	0.001	
	Dongshaoh	6m	3.472	1.408	8.565	2.702	0.007	
	hoher	6m	3.659	1.333	10.042	2.518	0.012	
Fixed			2.405	1.697	3.409	4.929	0.000	
Random			3.028	1.354	6.774	2.697	0.007	

Figure 2. Pooled results of re-stenosis rate of patients in PTCA groups and BMS groups.

Model	Study name	Subgroup within study	Statistics for each study					Odds ratio and 95% CI
			Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01 0.10 1.00 10.00 100.00
	Rahel	12m	3.370	1.483	7.660	2.901	0.004	
	Simes	6m	3.345	1.412	7.927	2.744	0.006	
	hoher	6m	2.000	0.769	5.198	1.422	0.155	
	Dongshaoh	6m	2.897	0.989	8.480	1.941	0.052	
	Rubartelli	9m	4.234	1.087	16.501	2.080	0.038	
Fixed			3.017	1.957	4.653	4.998	0.000	
Random			3.017	1.957	4.653	4.998	0.000	

Figure 3. Pooled results of subsequent PTCA rate of patients in PTCA groups and BMS groups.

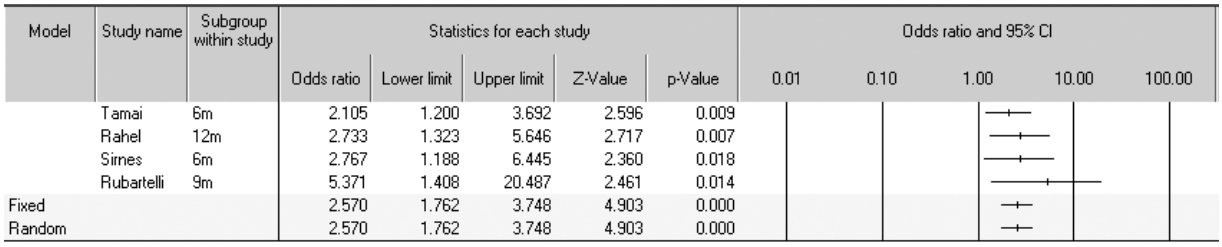

Figure 4. Pooled results of TLR of patients in PTCA groups and BMS groups.

CI, 4.192-33.355, $p < 0.001$, heterogeneity, Q = 24.590, $p < 0.001$ $I^2 = 83.733\%$) (Figure 8), TLR (OR, 4.343, 95% CI, 2.538-7.304, $p < 0.001$, heterogeneity, Q = 6.131, $p = 0.294$ $I^2 = 18.444\%$) (Figure 9) and TVR (OR, 2.983, 95% CI, 1.958-4.543, $p < 0.001$, heterogeneity, Q = 19.904, $p = 0.006$ $I^2 = 64.832\%$) (Figure 10), while lower MACE-free survival rate (HR, 0.699, 95% CI, 0.569-0.858, $p = 0.001$, heterogeneity, Q = 1.684, $p = 0.431$, $I^2 = 0.00\%$) (Figure 7). The other factors, including MI (OR, 1.164, 95% CI, 0.744~1.821, $p = 0.505$, heterogeneity, Q = 1.164, $p = 0.999$ $I^2 = 0.00\%$) and all cause death (OR, 1.081, 95% CI, 0.788-1.483, $p = 0.630$, heterogeneity, Q = 3.808, $p = 0.874$ $I^2 = 0.00\%$), did not show significant difference between DES groups and BMS groups.

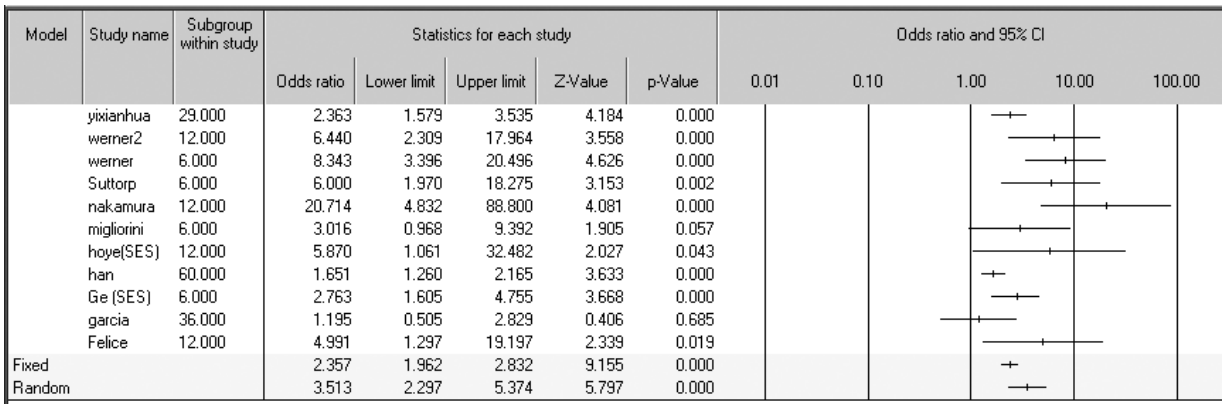

Figure 5. Pooled results of major adverse cardiac events of patients in BMS groups and DES groups.

Table II. Characteristics of 12 included studies.

Study	Year of publication	No. of patients	Sten type	Experiment protocol	Country	Occlusion time	Clinical follow-up (month)
Hoye et al.[26]	2004	84	SESvsBMS	Cohort study	Netherland	1	1
Werner et al.[27]	2004	96	PESvsBMS	Cohort study	Germany	>0.5	1
Ge Lei et al.[28]	2005	381	SESvsBMS	Cohort study	Italy	3	0.5
Nakamura et al.[29]	2005	180	SESvsBMS	Prospective	Japan	3	1
Werner et al.[30]	2006	164	PESvsBMS	Cohort study	Germany	>0.5	1
Suttorp et al.[31]	2006	200	SESvsBMS	RCT	Netherland	3	0.5
Migliorini et al.[32]	2006	100	DESvsBMS	Case-control	Italy	3	0.5
Garcia et al.[33]	2007	147	SESvsBMS	Cohort study	Netherland	3	3
Yixianhua	2008	1003	DESvsBMS	Cohort study	China	3	2.3
De Felice et al.[34]	2008	99	DESvsMS	Cohort study	Italy	3	1
De Felice et al.[35]	2009	221	DESvsBMS	Cohort study	Italy	3	1.5
Han et al.[36]	2009	930	DESvsBMS	Cohort study	China	3	5

Model	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	werner	6.000	16.927	0.945	303.301	1.921	0.055
	felice	18.000	3.085	0.609	15.627	1.361	0.174
	werner2	12.000	14.835	0.812	271.179	1.819	0.069
	Suttorp	6.000	2.020	0.180	22.645	0.570	0.568
Fixed			4.614	1.498	14.219	2.663	0.008
Random			4.614	1.498	14.219	2.663	0.008

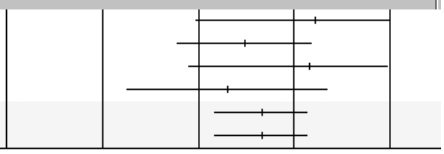

Figure 6. Pooled results of subsequent CABG rate of patients in BMS groups and DES groups.

Model	Study name	Subgroup within study	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
	han	60.000	0.733	0.579	0.928	-2.576	0.010
	Ge (SES)	6.000	0.529	0.326	0.859	-2.576	0.010
	garcia	36.000	0.857	0.391	1.877	-0.386	0.700
Fixed			0.699	0.569	0.858	-3.426	0.001
Random			0.699	0.569	0.858	-3.426	0.001

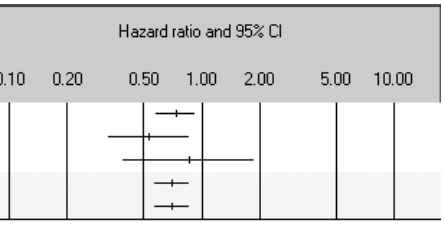

Figure 7. Pooled results of accumulated MACE-free survival rate of patients in BMS groups and DES groups.

Model	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	Ge (SES)	6.000	4.179	2.265	7.709	4.577	0.000
	Suttorp	6.000	31.909	14.243	71.489	8.414	0.000
	werner	6.000	22.241	8.573	57.699	6.378	0.000
	nakamura	12.000	36.676	4.912	273.851	3.512	0.000
	migliorini	6.000	3.490	1.345	9.057	2.569	0.010
Fixed			9.276	6.294	13.670	11.258	0.000
Random			11.825	4.192	33.355	4.669	0.000

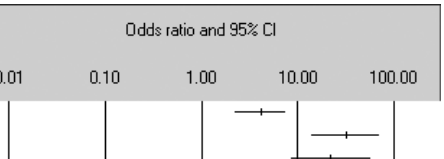

Figure 8. Pooled results of re-stenosis/re-occlusion rate of patients in BMS groups and DES groups.

Model	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	Ge (SES)	6.000	4.470	2.147	9.304	4.003	0.000
	nakamura	12.000	17.957	2.379	135.534	2.800	0.005
	felice	18.000	6.173	2.044	18.641	3.228	0.001
	Suttorp	6.000	5.630	1.840	17.220	3.029	0.002
	garcia	36.000	1.481	0.487	4.504	0.693	0.488
	Felice	12.000	3.659	0.701	19.102	1.538	0.124
Fixed			4.311	2.744	6.773	6.339	0.000
Random			4.343	2.583	7.304	5.538	0.000

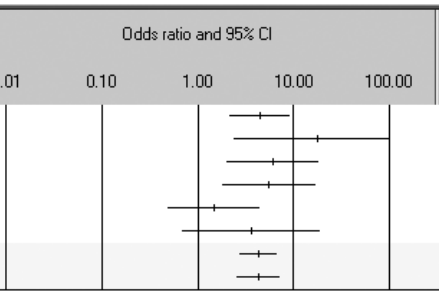

Figure 9. Pooled results of TLR of patients in BMS groups and DES groups.

Discussion

Clinical examination through coronary angiography has revealed that CTO exists in about half of the patients with coronary artery disease, also it is often accompanied with complex lesions in about 15% patients[14]. For treatment of CTOs, a lot of strategies and technologies have been developed but the success rate was not consistent in each presedure[15]. Although remarkable progress has been achieved to treat coronary artery disease recently[16], there is no systematic study that directly compared surgery cases of recanalization with different operation procedures. Therefore, in this

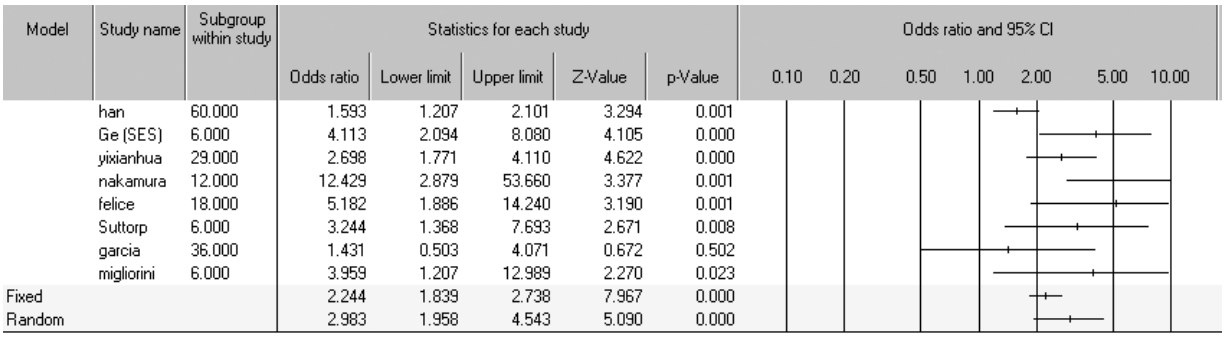

Figure 10. Pooled results of TVR of patients in BMS groups and DES groups.

study we systematically reviewed publications on the long term outcomes of several treatments in CTO patients, including PTCA, BMS and DES.

We analyzed seven articles on the long term outcomes between PTCA and BMS procedures. We found that four follow up variables as the incidence of re-occlusion, re-stenosis, subsequent PTCA and TLR were significantly lower for BMS implantation than for PTCA procedure. We also analyzed 12 articles on the long term outcomes between DES and BMS procedures. Variables as MACE, subsequent CABG, re-stenosis/re-occlusion rate were higher while accumulated MACE-free survival rate was significantly lower in BMS groups than in DES groups. All-cause death and recurrent myocardial infarction were not significantly different between the two groups. So, DES implantation is a better clinical treatment for revascularization compared to PTCA and BMS implantation, in reducing the rates of MACE, repeat operation and TLR, as well as in reducing the incidence of restenosis and re-occlusion. In our study, we did not found any difference in MI and all cause death, which may due to the low incidence of these two index. So studies with longer follow-up in the future are needed to confirm whether DES is superior to BMS in MI and all cause death.

Although argument stated that only the randomized trials should be included in the meta-analysis of intervention studies[17], since observational studies do not result in causal relationship, these studies still provide information with important message in certain circumstance[18]. Nevertheless, clinical phenomenon is observed in specific patients, the beneficial effects of DES in all these aspects observed in the first half year after surgery might be different in the far further. For a more confirmative conclusion, larger sample size and longer follow-up are needed for further research.

Conclusions

By analyzing the long term outcome of DES, PTCA and BMS treatment on CTO patients, we found that four follow up variables, including the incidence of re-occlusion, re-stenosis, subsequent PTCA and TLR, were significantly lower for BMS implantation than for PTCA procedure. Variables such as MACE, subsequent CABG, re-stenosis/re-occlusion rate were higher in BMS groups, while accumulated MACE-free survival rate was significantly lower in BMS groups than in DES groups.

Conflict of Interest

None to declare.

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