Transcatheter Mitral-Valve Repair in Patients with Heart Failure

G.W. Stone, et al, for the COAPT Investigators. September 23, 2018 at NEJM

BACKGROUND

Among patients with heart failure who have mitral regurgitation due to left ventricular dysfunction, the prognosis is poor. Transcatheter mitral-valve repair may improve their clinical outcomes.

METHODS

At 78 sites in the United States and Canada, we enrolled patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy. Patients were randomly assigned to transcatheter mitral-valve repair plus medical therapy (device group) or medical therapy alone (control group). The primary effectiveness end point was all hospitalizations for heart failure within 24 months of follow-up. The primary safety end point was freedom from device-related complications at 12 months; the rate for this end point was compared with a prespecified objective performance goal of 88.0%.

RESULTS

Of the 614 patients who were enrolled in the trial, 302 were assigned to the device group and 312 to the control group. The annualized rate of all hospitalizations for heart failure within 24 months was 35.8% per patient-year in the device group as compared with 67.9% per patient-year in the control group (hazard ratio, 0.53; 95% confidence interval [CI], 0.40 to 0.70; P<0.001). The rate of freedom from devicerelated complications at 12 months was 96.6% (lower 95% confidence limit, 94.8%; P<0.001 for comparison with the performance goal). Death from any cause within 24 months occurred in 29.1% of the patients in the device group as compared with 46.1% in the control group (hazard ratio, 0.62; 95% CI, 0.46 to 0.82; P<0.001).

CONCLUSIONS

Among patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy, transcatheter mitral-valve repair resulted in a lower rate of hospitalization for heart failure and lower all-cause mortality within 24 months of follow-up than medical therapy alone. The rate of freedom from device-related complications exceeded a prespecified safety threshold.

經導管二尖瓣修復在心衰竭患者 (COAPT trial)

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在左心室功能不良而具有二尖瓣逆流的心衰竭患者中，預後較差。經導管二尖瓣修復可改善其臨床結果。

方法

在美國和加拿大的 78 個中心，我們納入了心衰竭合併中度至重度或嚴重繼發性二尖瓣逆流，儘管使用了最大劑量的 guideline-directed medical therapy，但仍有症狀的患者。患者被隨機分配到經導管二尖瓣修復加藥物治療（device group）或單獨藥物治療（control group）。主要的有效 end point 為追蹤 24 個月內因心衰竭而住院。主要安全 end point 是在 12 個月內不發生 device 相關的併發症 (Table 2); 並將該 end point 的比率與預先設定的 88.0% 的客觀績效目標進行比較。

結果

在參加試驗的 614 名患者中，302 名被分配到 device group，312 名被分配到 control group。Device group 中 24 個月內發生心衰竭住院率的年化率為每患者年 35.8%，而 control group 為每患者年 67.9%（HR，0.53; 95%CI，0.40-0.70; P <0.001）(Figure A)。 12 個月時 device 相關併發症的 freedom rate 為 96.6% (lower 95% confidence limit, 94.8%; P<0.001 for comparison with the performance goal)(Figure B)。Device group 中患者在 24 個月內因任何原因死亡為 29.1%，而對照組為 46.1% （HR，0.62; 95% CI，0.46-0.82; P <0.001）(Figure C)。

討論

COAPT 試驗評估了經導管二尖瓣修復在心衰竭合併中度至重度或嚴重繼發性二尖瓣閉鎖不全患者的安全性和有效性，儘管使用了最大劑量的指引針對性藥物治療，但仍有症狀的患者。在該試驗中，使用 device 治療發生心衰竭再住院率顯著降低，死亡率降低，且追蹤 24 個月內的生活品質和功能均高於單獨的藥物治療。此外，經導管二尖瓣修復術中與 device 相關併發症的 freedom rate 超出了預先設定的客觀性能目標。許多次分析結果的益處亦是一致的，包括患有缺血性和非缺血性心肌病變的患者以及那些手術相關併發症或死亡風險高的患者，並且益處與起始的二尖瓣逆流等級和左心室容量及功能無關。

該試驗中使用的 MitraClip 是於 2013 年獲得美國食品和藥物管理局批准，用於治療高手術相關併發症或死亡風險的原發性二尖瓣閉鎖不全的患者。在美國，MitraClip 主要用於此適應症。但是，在美國以外，MitraClip 更常用於治療繼發性二尖瓣逆流的心衰竭患者。心衰竭和繼發性二尖瓣閉鎖不全患者的預後很差 ; 在這項試驗中，儘管使用了指引針對性的藥物治療，仍有大約三分之二的此類患者在 2 年內因心衰竭死亡或住院治療。MitraClip 治療之後可降低繼發性二尖瓣閉鎖不全的嚴重度 ; 這可能是患者預後，生活品質和功能能力改善的機制。值得注意的是，MitraClip 治療後 30 天內發生心衰竭的住院率較低 ; 較低的死亡率主要出現在治療 1 年後，一年後左心室容量超負荷持續降低的長期益處一致且延續。

在該試驗中，Clip 植入率為 98%，95% 的患者立即達到 2+ 或更低的二尖瓣逆流等級，遠遠優於 EVEREST II 於低風險患者的結果。此結果可能反映了操作者植入經驗增加和改善心臟超音波的指引。使用 MitraClip，二尖瓣逆流嚴重程度的降低也隨著時間持續可見。在 device group 中存活的患者中，2 年的二尖瓣閉鎖不全等級為 3+ 或更高，僅為 0.9%，2 + 或更高僅為 22.8%。相較之下，之前的一項隨機試驗評估縮小瓣環成形術環 (downsized annuloplasty ring) 在繼發性缺血性二尖瓣逆流患者中的有效

性，該患者的嚴重程度與本試驗中所見相似；在使用縮小的瓣環成形術環治療的存活患者中，2 年時二尖瓣關閉不全等級為 3+ 或更高的為 14.0%，58.8% 為 2+ 或更高。

COAPT trial 亦有一些研究侷限。首先，因為 MitraClip 在影像研究中是可見的，所以研究人員知道試驗組的分配。所以致力減輕偏差的方法包括嚴格的規定心臟超音波檢查程序，以及標準化指引性治療和使用獨立事件委員會及心臟超音波核心實驗室。雖然 device group 因心衰竭住院率較低，死亡率較低，且二尖瓣病變嚴重程度持續下降，生活品質和功能能力的提高和改進，該組都支持主要研究結果的有效性，儘管如此，仍不能完全排除潛在的偏見。第二，device group 追蹤時間的中位數長於對照組，部分原因是 device group 的死亡率較低。然而，對照組中退出試驗更為頻繁。在此對於缺失數據進行估算後，與主要結果是一致的。第三，renin-angiotension axis 的藥劑影響在 device group 的 baseline 使用頻率較高。在調整這些差異後，與主要研究結果仍是一致的。第四，為了充分表徵 MitraClip 的安全性和有效性，必須進行長達 5 年的長期追蹤。目前該分析的結果適用於 COAPT trial 中以 MitraClip 治療繼發性二尖瓣閉鎖不全；但是其他經導管手術方法或外科手術方法是否會有類似結果尚不確定。最後，所有納入的患者常伴有共存的情況包括儘管使用了最大劑量的指引性藥物治療（超過三分之一的患者接受了心臟再同步治療）仍然有症狀（NYHA II 級，III 級或 IVa [ambulatory]）並且具有中度至嚴重或嚴重的二尖瓣閉鎖不全以及 LVEF 為 20% 至 50%。但是，MitraClip 對於臨床病情較輕或再更加嚴重的患者，或二尖瓣逆流不太嚴重的患者是否具有相似的益處尚不得而知。

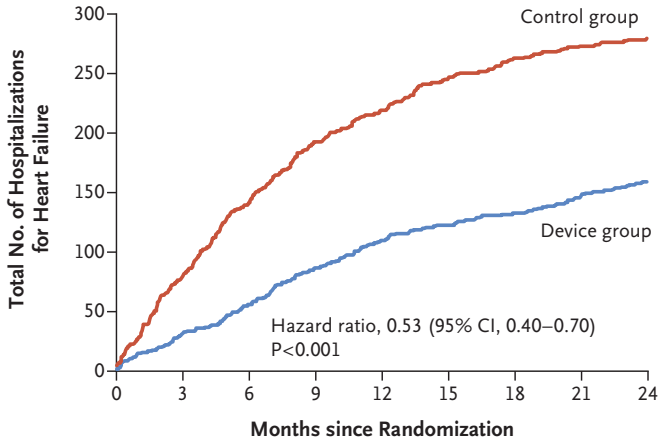
結論

在心衰竭合併中重度或嚴重繼發性二尖瓣逆流，儘管使用最大劑量的指引針對性藥物治療仍有症狀的患者中，經導管二尖瓣修復後發生心衰竭住院率較低，且追蹤 24 個月內的全因死亡率也低於單獨的藥物治療。與 device 相關併發症的 freedom rate 也超過了預定的安全閾值。

Table 2. Primary and Secondary End Points.*

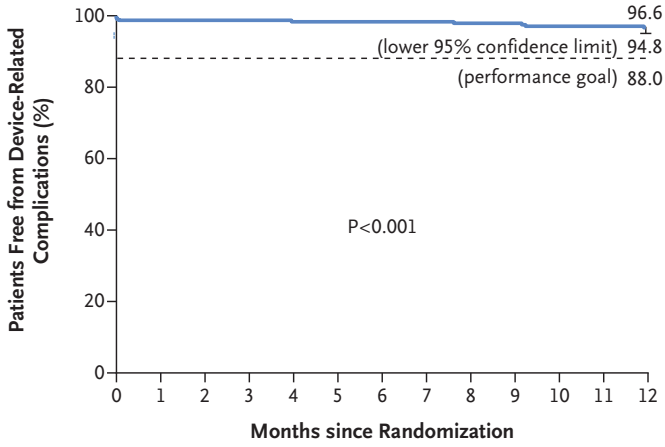
End Point	Device Group (N=302)	Control Group (N=312)	Hazard Ratio (95% CI)	P Value†
Primary				
Effectiveness: all hospitalizations for heart failure within 24 mo — no. of events/total no. of patient-yr (annualized rate)	160/446.5 (35.8)	283/416.8 (67.9)	0.53 (0.40 to 0.70)‡	<0.001§
Safety: freedom from device-related complications at 12 mo — Kaplan–Meier estimate of event-free rate (lower 95% confidence limit)	96.6 (94.8)	—	—	<0.001 for comparison with goal of 88.0%¶
Secondary, listed in hierarchical order				
Mitral regurgitation grade of 2+ or lower at 12 mo — no./total no. (%)‖	199/210 (94.8)	82/175 (46.9)	—	<0.001**
Death from any cause at 12 mo — no. of events (Kaplan–Meier estimate of event rate)	57 (19.1)	70 (23.2)	0.81 (0.57 to 1.15)††	<0.001 for noninferiority‡‡
Death or hospitalization for heart failure within 24 mo	—	—	—	<0.001§§
Change in KCCQ score from baseline to 12 mo — points¶¶	12.5±1.8	−3.6±1.9	16.1 (11.0 to 21.2)‖‖	<0.001***
Change in distance on 6-min walk test from baseline to 12 mo — m†††	−2.2±9.1	−60.2±9.0	57.9 (32.7 to 83.1)‖‖	<0.001***
All hospitalizations for any cause within 24 mo — no. of events/total no. of patient-yr (annualized rate)	474/446.5 (106.2)	610/416.8 (146.4)	0.76 (0.60 to 0.96)	0.02§
NYHA functional class of I or II at 12 mo — no./total no. (%)	171/237 (72.2)	115/232 (49.6)	—	<0.001**
Change in left ventricular end-diastolic volume from baseline to 12 mo — ml	−3.7±5.1	17.1±5.1	−20.8 (−34.9 to −6.6)‖‖	0.004***
Death from any cause within 24 mo — no. of events (Kaplan–Meier estimate of event rate)	80 (29.1)	121 (46.1)	0.62 (0.46 to 0.82)	<0.001‡‡‡
Freedom from death from any cause, stroke, myocardial infarction, and nonelective cardiovascular surgery for a device-related complication at 30 days — % (lower 95% confidence limit)	96.9 (94.7)	—	—	<0.001 for comparison with goal of 80.0%**

A Hospitalization for Heart Failure



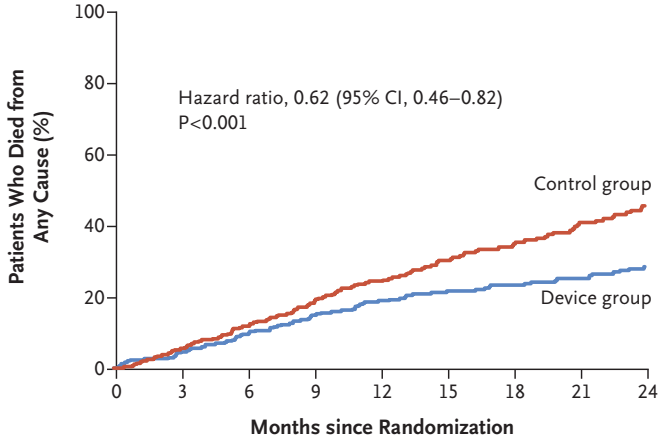
No. at Risk									
Control group	312	294	271	245	219	176	145	121	88
Device group	302	286	269	253	236	191	178	161	124

B Freedom from Device-Related Complications



No. at Risk													
Device group	293	283	282	277	272	269	261	258	251	245	241	236	221

C Death from Any Cause



No. at Risk									
Control group	312	294	271	245	219	176	145	121	88
Device group	302	286	269	253	236	191	178	161	124

Table 3. Adverse Events within 24 Months in the Intention-to-Treat Population.*

Event	Device Group (N=302)	Control Group (N=312)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (Kaplan–Meier estimate of event rate)			
Death from any cause	80 (29.1)	121 (46.1)	0.62 (0.46–0.82)	<0.001
Cardiovascular cause	61 (23.5)	97 (38.2)	0.59 (0.43–0.81)	0.001
Related to heart failure	28 (12.0)	61 (25.9)	0.43 (0.27–0.67)	<0.001
Not related to heart failure	33 (13.1)	36 (16.6)	0.86 (0.54–1.38)	0.53
Noncardiovascular cause	19 (7.3)	24 (12.7)	0.73 (0.40–1.34)	0.31
Hospitalization for any cause	194 (69.6)	228 (81.8)	0.77 (0.64–0.93)	0.01
Cardiovascular cause	138 (51.9)	180 (66.5)	0.68 (0.54–0.85)	<0.001
Related to heart failure	92 (35.7)	151 (56.7)	0.52 (0.40–0.67)	<0.001
Not related to heart failure	72 (29.4)	72 (31.0)	0.98 (0.71–1.36)	0.92
Noncardiovascular cause	124 (48.2)	128 (52.9)	0.91 (0.71–1.17)	0.47
Death or hospitalization for heart failure	129 (45.7)	191 (67.9)	0.57 (0.45–0.71)	<0.001
Death from cardiovascular cause or hospitalization for heart failure	117 (42.7)	177 (63.6)	0.56 (0.44–0.70)	<0.001
Unplanned mitral-valve intervention	10 (4.0)	15 (9.0)	0.61 (0.27–1.36)	0.23
MitraClip implantation	9 (3.7)	8 (6.6)	0.99 (0.38–2.58)	0.99
Mitral-valve surgery	1 (0.4)	7 (2.5)	0.14 (0.02–1.17)	0.07
PCI or CABG	7 (2.8)	13 (4.3)	0.62 (0.24–1.60)	0.32
PCI	7 (2.8)	11 (3.6)	0.75 (0.28–2.02)	0.57
CABG	0	2 (0.7)	—	—
Stroke	11 (4.4)	11 (5.1)	0.96 (0.42–2.22)	0.93
Myocardial infarction	12 (4.7)	14 (6.5)	0.82 (0.38–1.78)	0.62
New cardiac resynchronization therapy	7 (2.9)	8 (3.3)	0.85 (0.31–2.34)	0.75
LVAD implantation or heart transplantation	9 (4.4)	22 (9.5)	0.37 (0.17–0.81)	0.01
LVAD implantation	6 (3.0)	16 (7.1)	0.34 (0.13–0.87)	0.02
Heart transplantation	3 (1.4)	8 (3.6)	0.35 (0.09–1.32)	0.12