Early pacemaker implantation in Transcatheter aortic valve implantation is safe and effective

Kush P Patel[1,2], Wei Yao Lim[1], Asha Pavithran[1], Rangeena Assadi[1], Daniel Wan[1], Simon Kennon[1], Mick Ozkor[1], Mark Earley[1], Simon Sporton[1], Mehul Dhinoja[1], Carl Hayward[1], Amal Muthamala[1], Ross Hunter[1,3], Martin Lowe, Pier Lambiase[1,3], Oliver Segal[1], Anthony Mathur [1,3], Richard Schilling[1,3], Andreas Baumbach[1,3,4], Michael J Mullen[1], Anthony WC Chow[1,3]

1. Barts Heart Centre, St Bartholomew's Hospital, West Smithfield, London, EC1A 7BE
2. Institute of Cardiovascular Science, University College London, UK.
3. Centre for Cardiovascular Medicine and Devices, William Harvey Research Institute, Queen Mary University of London and Barts Heart Centre, London, United Kingdom
4. Yale University School of Medicine, New Haven, USA

Corresponding author
Dr Anthony WC Chow
Barts Heart Centre, St Bartholomew's Hospital,
West Smithfield, London, UK,
EC1A 7BE
+442073777000
anthony.chow1@nhs.net

Word count- 2380

Abstract

Introduction

Cardiac conduction abnormalities and permanent pacemaker (PPM) implantation are common complications of transcatheter aortic valve implantation (TAVI). Guidelines on pacing for TAVI patients advocate a period of observation of up to 7 days before PPM implantation. This has important implications for the patient and healthcare providers. This study aimed to assess the safety and efficacy of early PPM implantation without an observation period, among TAVI patients.

Methods

This is a retrospective, observational, single-centre study of 1398 TAVI patients between January 2016 and September 2019. Clinical and pacing data was collected at baseline, 30 days and at a median of 15 (4-21) months post-TAVI. Safety and efficacy were evaluated by examining PPM-related complications, pacing utilisation (defined as percentage pacing >1% or pacing at the time of the pacing check) and hospital length of stay.

Results

105 patients (8.2%) required a PPM, of which 13 had pre and 92 had post-TAVI implantation. 76% of patients had PPM implanted because of either second or third degree heart block. Median time to implantation for post-TAVI PPM was 1 day (0-3) post-TAVI. 6 patients (5.7%) experienced a pacing-related complication- 3 had a lead displacement, 2 developed a haematoma and 1 developed a device infection. Pacing utilisation was 79% at 30 days and 81% at a median of 15 months. Multivariate analysis revealed complete heart block was the only independent predictor of pacing utilisation. Hospital length of stay for the post-TAVI pacing group was longer than the group without PPM (4 (2-8) vs 3 (2-4) days; $p<0.001$).

Conclusion

Early PPM implantation in TAVI patients is safe with a low complication rate, with the majority of patients requiring pacing in the short and mid-term. Additionally, it reduces length of hospital stay compared to guideline recommendations.

Key words: pacing utilisation, permanent pacemaker, transcatheter aortic valve implantation, TAVI, TAVR

Introduction

Transcatheter aortic valve implantation (TAVI) is increasingly used as the predominant treatment for aortic valve stenosis (AS) [1], [2]. Disturbances in cardiac conduction are a well-recognised complication following TAVI and necessitate the implantation of a permanent pacemaker (PPM) in 2-51% of patients [3]. Many conduction abnormalities tend to evolve over time; some recovering and others deteriorating, with a minority experiencing changes >48 hours post-TAVI or after discharge [4], [5]. This makes it challenging to decide the optimal timing of permanent pacing. Additionally, a PPM has consequences for the patient, with long-term risks of device and lead-related complications and the potential of developing left ventricular dysfunction [6]–[8].

Current guidelines recommend PPM implantation for high degree and complete atria-ventricular (AV) block, with a 7-day period of monitoring to assess whether a conduction disturbance is transient. Guidance for other forms of conduction abnormalities are not provided [9]. Consequently, there is a large degree of variability in the timing and indication of PPM implantation between centres. Recently, expert consensus has provided proposals for prolonged in-hospital and post-discharge electrocardiographic (ECG) monitoring, the use of temporary pacing and performing electrophysiological (EP) studies [10]. Whilst these additional proposals are useful, their exact role in predicting need for long term pacing remain uncertain.

Implantation of a PPM is of paramount importance in TAVI for three reasons; TAVI rates are set to expand as indications extend to low risk groups and the incidence of significant AS increases [11], [12]. Secondly, as life expectancy increases [13] and TAVI is used in younger patients, PPM related complications and device revisions will increase. Lastly, most recognised complications of TAVI have reduced, with the exception of PPM implantation rate, which has remained stable or in some cases has increased [3], [14]. A balance needs to be struck between early PPM implantation to facilitate hospital discharge and conservative monitoring with recovery of conduction abnormalities to avoid unnecessary PPM implantation and its associated complications.

At our institution we have adopted a policy of early PPM implantation in patients where it is deemed necessary. This study evaluates the safety and efficacy of early PPM implantation post-TAVI by assessing the impact on complications, hospital length of stay and pacing utilisation.

Methods

Study population

This is a retrospective observational study at a single, high-volume tertiary cardiac centre that included all patients who had a TAVI for severe AS between January 2016 and September 2019. Local ethics approval was obtained for this study

Pre-procedural evaluation

All patients had a transthoracic echocardiogram, a gated cardiac computed tomography scan and an ECG pre-TAVI. Patients were discussed at a multi-disciplinary team meeting to review the diagnosis and consider the most appropriate management strategy.

Procedures

Both TAVI and PPM implantation were performed by experienced structural interventionists and electrophysiologists respectively, following standard implant techniques. All TAVIs were performed with full heparinisation, which was reversed at the end of the procedure using protamine. Patients received dual antiplatelet agents post-TAVI. The choice of valve technology and PPM were at the discretion of the operator. The decision to implant a PPM was based on a case-by-case basis and was decided either within a multi-disciplinary team meeting, pre-TAVI or between the clinicians and the patient, post-TAVI. It is our departmental policy for early PPM implantation post-TAVI.

Device programming and follow-up

Devices were programmed DDD 50-60bpm with algorithms to minimise ventricular pacing (MVP), or VVI pacing if patients were bradycardic with slow AF. Patients had an initial pacing check at 1 month, 6 months then 12 months and then every subsequent year post-PPM implant. Some patients had follow-up elsewhere for geographical convenience and consequently the follow up period may have varied. Data for these patients was obtained by calling the respective pacing centres and requesting data of the pacing checks. The amount of pacing utilisation was obtained at 1 month and at the patient's latest follow-up.

Data collection

Demographic, clinical, imaging and pacing data was prospectively collected for all patients onto a local database. Where pacing checks were conducted at a different centre, pacing data

was obtained via telephone. We defined pacemaker utilisation as ventricular or atrial pacing time pacing time >1% or pacing at the time of the pacing check.

Statistical analysis

Data are presented as frequency (percentages), or medians (interquartile range) as appropriate. Inter-group comparisons were made using χ^2 test or Fisher's exact test for categorical data, and Mann Whitney U-tests for continuous data. A binary logistic regression analysis was carried out to assess independent predictors of pacing utilisation. Parameters thought to influence pacing utilisation were decided a priori and included indication for PPM implantation, type of TAVI valve, procedural balloon aortic valvuloplasty and post-dilatation of the TAVI valve. Data were analysed using SPSS (version 13.0, V26, IBM, Chicago, IL) and a two-sided p value < 0.05 was considered statistically significant.

Results

Study population

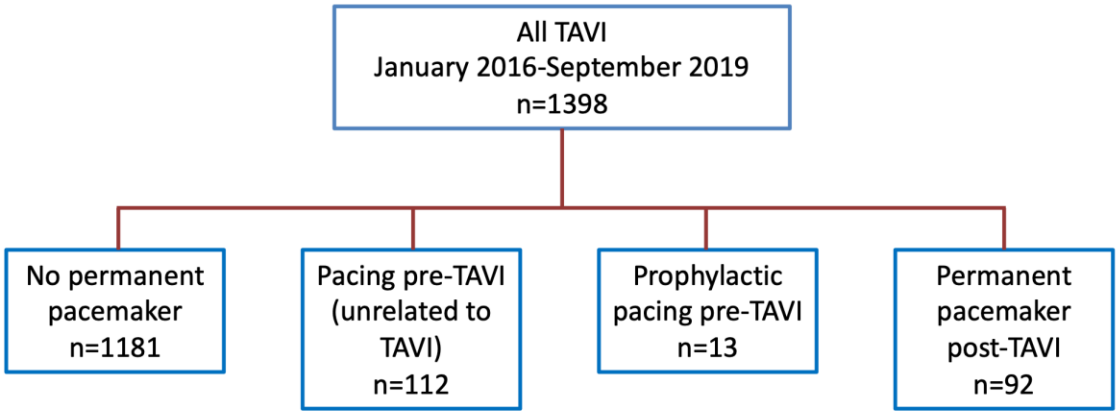

Figure 1: Study population. Patients with pacing unrelated to TAVI were not used in this study (n=112).

For this study we examined the two groups who had a permanent pacemaker implanted either prophylactically pre-TAVI or post-TAVI (n=105) and compared them to patients without any pacemakers (n=1181) (figure1).

Baseline characteristics

Patient characteristics at baseline are shown in table 1. The median age of the study population was 83 (78-87) years, 47.8% male with severe AS. Patients who needed a PPM had more males (61 vs 50%; p=0.025), had a lower mean aortic valve gradient (40 (35-46) vs 43 (35-51); p=0.036) and had a higher Logistic Euroscore (15.2 (9.1-21.8) vs 12.5 (8.0-20.6); p=0.046). Overall PPM implantation rate was 8.2% in our study.

Variable	**No pacemaker (n=1181)**	**Pacemaker implanted (n=105)**	**P value**
Demographics			
Age (years)	83 (78-87)	84 (81-88)	0.104
Sex (% male)	50	61	0.025
AS severity			
Mean aortic valve gradient (mmHg)	43 (35-51)	40 (35-46)	0.036
Aortic valve area (cm2)	0.7 (0.6- 0.8)	0.7 (0.6- 0.8)	0.420
Comorbidities			
Logistic Euroscore	12.5 (8.0-20.6)	15.2 (9.1- 21.8)	0.046
eGFR (mg/dL)	57 (43- 69)	57 (41-75)	0.940
Hypertension (%)	824 (76.9)	84 (81.6)	0.278
Diabetes (%)	272 (23.3)	33 (30.3)	0.102
Previous MI (%)	159 (15.0)	16 (15.5)	0.876
Pulmonary disease (%)	234 (22.1)	20 (19.4)	0.527
LVEF>50% (%)	763 (75.1)	71 (72.4)	0.488

Table 1: Baseline characteristics of patients comparing those without a pacemaker to those with a pacemaker. eGFR- estimated glomerular filtration rate, MI, myocardial infarction, LVEF- left ventricular ejection fraction

TAVI procedure

There were differences in the types of valves used between patients with PPM implanted and those without PPM. Procedural balloon valvuloplasty and post-dilatation were similar between both groups (Table 2).

Variable	**No pacemaker (n=1181)**	**Pacemaker implanted (n=105)**	**P value**
Balloon expandable valve	956 (81%)	61 (58%)	<0.005
Mechanical expandible/other valve	112 (9%)	20 (19%)	
Self-expanding valve	113 (10%)	24 (23%)	
Procedural balloon valvuloplasty	232 (20%)	26 (25%)	0.407
Post-dilatation	45 (4%)	5 (5%)	0.847

Table 2: TAVI procedural details

Permanent pacemaker implantation

Median time from TAVI to PPM implantation in the post-TAVI pacing group was 1 (0, 3) day. Median procedural duration was 63 (45-85) minutes. Table 3 shows the type of devices implanted.

Type of PPM	**Number (n=105)**	**Percentage**

Cardiac resynchronisation therapy	7	7%
Dual chamber device	67	64%
Leadless pacemaker (MicraTM)	1	1%
Single chamber device	30	28%

Table 3: Type of PPM implanted

Hospital length of stay

Patients who required a PPM post-TAVI had a significantly longer hospital length of stay compared to those who required prophylactic pacing or no pacing (table 4). All patients in this cohort had a PPM implant during the same admission as their TAVI.

	No pacing	**Prophylactic pre-TAVI pacing**	**Post-TAVI pacing**	**P value**
Hospital length of stay	3 (2-4) *	2 (2-4) #	4 (2-8)	<0.001

Table 4: Hospital length of stay was significantly longer in the post-TAVI pacing group compared to both prophylactic pacing and no pacemaker group.

P=0.013 between post-TAVI pacing group and no prophylactic pre-TAVI pacing group

* P<0.001 between post-TAVI pacing group and no pacing group

Complications

6 patients (5.6%) developed device-related complications; 3 right ventricular lead displacements that required replacement, 2 haematomas treated conservatively and 1 device infection, which required removal of the infected device, surgical wound debridement, antibiotics and replacement of a new PPM.

Pacemaker utilisation

The majority of PPM were implanted for high degree heart block (76%), of which complete heart block (CHB) was the most common indication. At 30 days pacing data was available for (n=81) 77% of patients and revealed pacemaker utilisation in (n=64) 79% of these patients. At a median of 15 (4-23) months, pacing data was available in (n=78) 74% of patients and revealed pacemaker utilisation in (n=63) 81% of these patients. Overall pacing utilisation at any time point was (n=89) 88% amongst 102 patients, where pacing checks were available (table 5). In a multivariate model, only CHB was identified as an independent predictor of pacing utilisation (supplementary table 1).

For patients with a prophylactic PPM (n=13), pacing data was available in 7 patients at 30 days of which 5 were utilising their PPM. At a median of 15 months, pacing data was available in 10 patients of which 8 were utilising their PPM. Overall, 11 patients utilised their PPM at some point.

Indications for pacing	**Number of patients**	**Prophylactic pre-TAVI PPM insertion**	**pacing at 1 month**	**pacing at median 15 months**	**Pacing at some point**
Complete heart block	75	1	51/60	48/54	68/73
Second degree heart block	5	0	2/4	2/5	3/5
Trifascicular block	10	6	4/7	4/7	5/9
Sinus node disease	7	1	5/6	3/5	6/7
Alternating LBBB and RBBB	2	0	1/1	1/2	2/2

Other	6	5	1/3	5/5	5/5
Totals	105	13	64/81 (79%)	63/78 (81%)	89/101 (88%)

Table 5: Pacing indications. This table shows the number of patients with pacing checks at various time points post-PPM implantation (denominator) and of those, the number of patients who were pacing >1% of the time or pacing dependant at the time of a pacing check (numerator). LBBB- left bundle branch block, RBBB- right bundle branch block.

Underlying rhythm in patients with high degree heart block

Among 80 patients with an initial PPM indication for either complete or second-degree heart block, pacing data was available in 59 patients at a median of 15 (4-23) months. The underlying rhythm in 31 patients (53%) at the time of the pacing check, was not complete or second-degree heart block.

Discussion

This study has demonstrated 3 key findings; firstly, early PPM implantation is safe with few complications. Secondly, it is effective as 88% of patients required pacing post implant. Lastly, although it increases hospital length of stay marginally compared to those who do not need a PPM, it would still reduce overall hospital stay when compared to guideline recommendations [9].

Although guidelines on pacing exist for TAVI patients [9], there remains a large degree of variability in practice between centres [10]. This study evaluated the safety and effectiveness of early PPM implantation in a high volume tertiary centre. In keeping with a recent expert consensus for procedural/persistent CHB [10], we implant PPM early (median: 1 day) post-TAVI in most patients, rather than maintain temporary pacing and prolonged monitoring as per guidelines [9]. During follow up 89% of this group continued to utilise their pacemaker in the mid-term and 93% required pacing at some point. This high degree of pacing utilisation is in keeping with a small study evaluating pacing percentage among patients without conduction abnormalities pre-TAVI, who develop persistent complete or second-degree

mobitz type 2 AV block. PPM implantation was at a similar time to our study: median 1 (0-1) day post-TAVI. 85% of patients had a ventricular pacing rate >40% at 1 year post-PPM. The study also demonstrated that patients with transient complete or second degree AV block have lower pacing utilisation; 33% of patients had a ventricular pacing rate >40% at 1 year [15].

However, 7% of patients in our study with CHB, did not require pacing, suggesting that even CHB can resolve over time. Supporting this finding is our data on the underlying rhythm among patients with an initial PPM indication of either complete or second degree heart block. In half of these patients, the underlying rhythm at the mid-term pacing check was not complete or second degree heart block. Similar findings have been noted by other studies [16], [17]. Early PPM implantation was also performed for other indications, with variable effectiveness (table 4). Although our understanding of conduction abnormalities that develop after valve interventions has improved, predicting who and when pacing will need remains a challenge, as conduction abnormalities can change over time [18], consequently questioning the concept of early or late pacing intervention. Multivariate analysis revealed only CHB, as an indication for PPM implantation as best practice. Further studies are required to confirm our findings and identify other predictors that influence pacing utilisation. Overall pacing utilisation remained high in our entire cohort (88% at some point required pacing). Among the cohort with prophylactic PPM implantation, pacing utilisation at some point was similar (85%).

Several studies have addressed pacing dependency post-TAVI. This is often defined by the intrinsic underlying rhythm during a pacing check when the pacing threshold is lowered. However, this provides data at a single time point, whereas among TAVI patients, it is well known that conduction abnormalities evolve [18] and a broader assessment of pacing use over time provides more clinically meaningful data. Our rates of pacing utilisation differ to reported rates of pacing dependency; 32-44% at 30 days [17]–[19] and 50% at 1 year post-TAVI [19].

Our study demonstrates low procedural complication rates among patients who underwent early PPM implantation. The use of anticoagulation during a TAVI and dual antiplatelet agents post-TAVI can increase the risk of bleeding. However, only 2 patients developed PPM-related haematomas, and both were managed conservatively. Our routine practice is to

use protamine to reverse heparinisation post-TAVI and use diathermy during PPM implantation. In addition, at day 1 post-TAVI when majority of PPM were implanted, the maximum inhibition of dual antiplatelet agents may not have been reached [20]. These aspects are likely to have reduced the risk of bleeding.

Our findings have important implications for patients and healthcare providers. Although patients with PPM had marginally longer hospital length of stays compared to those without PPM, it was still considerably shorter than guideline recommendations. By implanting PPM early post-TAVI, early discharge can be facilitated, whilst optimising procedural safety and efficacy. This has benefits for patients and considerable cost savings for healthcare providers [21].

Conclusions

Early PPM implantation post-TAVI is safe and effective with low complication and high pacing utilisation rates. Future studies need to identify other predictors of pacing utilisation, in order to facilitate early PPM implantation in those who need it and discharge in those who do not.

Limitations

This was a single centre, retrospective, observational study therefore certain biases will exist. Apart from CHB, there were few patients with other indications for a PPM, thus limiting our ability to assess pacing utilisation for other indications. A limited number of parameters were available for identifying predictors of pacing utilisation. Therefore, future prospective studies are required to confirm our findings. Pacing utilisation is dependent on the particular programming of the device. Whilst all devices are programmed to promote intrinsic rhythm as much as possible, this can lead to differing pacing utilisation rates between studies.

Supplementary index

A binary logistic regression analysis was performed to determine predictors of pacing utilisation among 94% of patients with pacemakers, where a complete dataset existed. Procedural variables considered important were included in the model.

Variable		95% Confidence interval	P value

	Odds ratio	Lower	Upper	
Complete heart block	**17.6**	**2.7**	**114.5**	**0.003**
Second degree heart block	1.4	0.1	13.9	0.817
Sinus node dysfunction	5.5	0.4	70.1	0.222
Mechanical	1.0	0.1	8.2	0.884
Self-expanding valve	0.7	0.1	4.5	0.652
Procedural BAV	0.4	0.1	2.5	0.808
Post dilatation	0.7	0.0	11.3	0.366

Supplementary table 1: Binary logistic regression of patients with a PPM to determine predictors of pacing utilisation.

References

[1] M. Alkhouli, F. Alqahtani, K. M. Ziada, S. Aljohani, D. R. Holmes, and V. Mathew, "Contemporary trends in themanagement of aortic stenosis in the USA," *Eur. Heart J.*, 2020, doi: 10.1093/eurheartj/ehz568.

[2] C. Costa, Giuliano; Barbanti, Marco; Tamburino, "Trends in European TAVI Practice," *Card. Interv. today*, 2018.

[3] V. Auffret *et al.*, "Conduction disturbances after transcatheter aortic valve replacement: Current status and future perspectives," *Circulation*. 2017, doi: 10.1161/CIRCULATIONAHA.117.028352.

[4] S. Toggweiler *et al.*, "The Electrocardiogram After Transcatheter Aortic Valve Replacement Determines the Risk for Post-Procedural High-Degree AV Block and the Need for Telemetry Monitoring," *JACC Cardiovasc. Interv.*, 2016, doi: 10.1016/j.jcin.2016.03.024.

[5] P. J. Khatri *et al.*, "Adverse effects associated with transcatheter aortic valve implantation: A meta-analysis of contemporary studies," *Annals of Internal Medicine*. 2013, doi: 10.7326/0003-4819-158-1-201301010-00007.

[6] M. Urena *et al.*, "Permanent pacemaker implantation after transcatheter aortic valve implantation impact on late clinical outcomes and left ventricular function," *Circulation*, 2014, doi: 10.1161/CIRCULATIONAHA.113.005479.

[7] J. W. M. Van Eck *et al.*, “Incidence and predictors of in-hospital events after first implantation of pacemakers,” *Europace*, 2007, doi: 10.1093/europace/eum113.

[8] F. Eberhardt *et al.*, “Long term complications in single and dual chamber pacing are influenced by surgical experience and patient morbidity,” *Heart*, 2005, doi: 10.1136/hrt.2003.025411.

[9] M. Brignole *et al.*, “2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy The Task Force on cardiac pacing and resynchronization therapy of the,” *Eur. Heart J.*, 2013.

[10] J. Rodés-Cabau *et al.*, “Management of Conduction Disturbances Associated With Transcatheter Aortic Valve Replacement: JACC Scientific Expert Panel,” *Journal of the American College of Cardiology*. 2019, doi: 10.1016/j.jacc.2019.07.014.

[11] A. P. Durko *et al.*, “Annual number of candidates for transcatheter aortic valve implantation per country: current estimates and future projections,” *Eur. Heart J.*, 2018, doi: 10.1093/eurheartj/ehy107.

[12] J. L. D’Arcy *et al.*, “Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: The OxVALVE Population Cohort Study,” *Eur. Heart J.*, 2016, doi: 10.1093/eurheartj/ehw229.

[13] WHO, “Life Expecatancy and Healthy life expectancy.” https://www.who.int/data/gho/data/themes/topics/indicator-groups/indicator-group-details/GHO/life-expectancy-and-healthy-life-expecancy.

[14] F. De Torres-Alba *et al.*, “Changes in the Pacemaker Rate after Transition from Edwards SAPIEN XT to SAPIEN 3 Transcatheter Aortic Valve Implantation the Critical Role of Valve Implantation Height,” *JACC Cardiovasc. Interv.*, 2016, doi: 10.1016/j.jcin.2015.12.023.

[15] L. Junquera *et al.*, “Intraprocedural high-degree atrioventricular block or complete heart block in transcatheter aortic valve replacement recipients with no prior intraventricular conduction disturbances,” *Catheter. Cardiovasc. Interv.*, 2020, doi: 10.1002/ccd.28323.

[16] A. D. Simms *et al.*, “Ongoing requirement for pacing post-transcatheter aortic valve implantation and surgical aortic valve replacement,” *Interact. Cardiovasc. Thorac. Surg.*, 2013, doi: 10.1093/icvts/ivt175.

[17] R. M. A. Van Der Boon *et al.*, “Pacemaker dependency after transcatheter aortic valve implantation with the self-expanding medtronic core valve system,” *Int. J. Cardiol.*, 2013, doi: 10.1016/j.ijcard.2012.11.115.

[18] E. Sharma *et al.*, “Aortic Valve Calcification as a Predictor of Post-Transcatheter Aortic Valve Replacement Pacemaker Dependence,” *Cardiol. Res.*, vol. 11, no. 3, pp. 155–167, Jun. 2020, doi: 10.14740/cr1011.

[19] C. U. Meduri *et al.*, “Pacemaker Implantation and Dependency After Transcatheter Aortic Valve Replacement in the REPRISE III Trial,” *J. Am. Heart Assoc.*, 2019, doi: 10.1161/JAHA.119.012594.

[20] A. O. Maree and D. J. Fitzgerald, “Variable platelet response to aspirin and clopidogrel in atherothrombotic disease,” *Circulation*, 2007, doi: 10.1161/CIRCULATIONAHA.106.675991.

[21] P. Kortebein, A. Ferrando, J. Lombeida, R. Wolfe, and W. J. Evans, “Effect of 10 days of bed rest on skeletal muscle in healthy older adults [8],” *Journal of the American Medical Association*. 2007, doi: 10.1001/jama.297.16.1772-b.