# The effect of everolimus vs calcineurin inhibitors on left ventricular mass in de novo heart transplant recipients after 3 years follow-up

## Results from the randomized controlled SCHEDULE Trial

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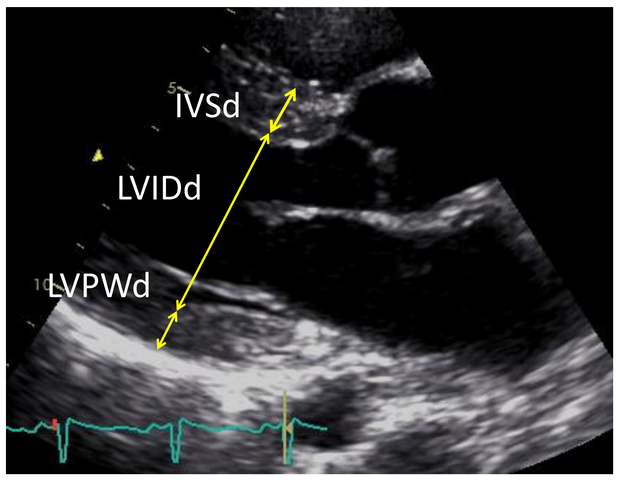
## BACKGROUND

Cardiac allograft hypertrophy is common after heart transplantation (HTX) and associated with increased long-term mortality. Post-transplant hypertension, kidney failure, vasculopathy and allograft hypertrophy has been attributed to treatment with calcineurin inhibitors. Inhibitors of the mechanistic target of rapamycin (mTOR) may have beneficial effects on cardiac function and reduce left ventricular mass (LVM) in HTX. However, the effect of mTOR inhibitors on LVM remains unknown in *de novo* HTX.

## METHODS

In the SCHEDULE-trial we randomized de novo heart transplant recipients to early conversion to everolimus (EVR) vs cyclosporine (CyA). We performed echocardiography at 7 weeks, 1 year and 3 years. LVM was estimated according to the Devereux formula and divided by body surface area to give LVM index (Figure 1). We used mixed models to assess the changes in LVM index between the treatment arms during follow-up. Left ventricular hypertrophy (LVH) was defined as an LVM index > 115 g/m² in males and > 95 g/m² in females according to guidelines. All images were analyzed by an experienced sonographer (RM), to avoid interobserver variability.

**Figure 1. Parasternal long axis view**




*LVM was calculated according to the Devereux formula: 0.8 x {1.04 [([LVIDd + IVSd + LVPWd]³- LVIDd³)]} + 0.6 and divided by body surface area to give LVM index. LV dimensions were measured in the parasternal long axis view in end-diastole, as illustrated in the figure. IVSd represents the thickness of intraventricular septum, LVIDd the inner dimension of the LV and LVPWd the thickness of the posterior wall of the LV.*

**Table 2. Baseline (7 weeks post-transplant) echocardiography**

| Variable | Everolimus (n = 38) | Cyclosporine (n = 45) |
|---|---|---|
| **Cardiac Structure** | | |
| IVSd (mm) | 11.3 ± 1.7 | 11.0 ± 1.4 |
| LVPWd (mm) | 9.6 ± 1.4 | 9.4 ± 1.2 |
| LVIDd (mm) | 47.6 ± 4.7 | 48.4 ± 4.7 |
| LVM (g) | 180 ± 49 | 179 ± 44 |
| LVMI (g/m²) | 94 ± 21 | 89 ± 18 |
| **Diastolic Function** | | |
| EA-ratio | 2.0 ± 0.8 | 2.3 ± 0.9 |
| MV E (cm/s) | 79 ± 16 | 78 ± 15 |
| MV A (cm/s) | 44 ± 15 | 37 ± 11 |
| EdecT (ms) | 169 ± 37 | 175 ± 41 |
| e'lateral (cm/s) | 10.6 ± 3.3 | 10.7 ± 2.3 |
| e'septal (cm/s) | 6.6 ± 1.5 | 6.5 ± 1.6 |
| E/e' ratio | 10.2 ± 4.0 | 9.5 ± 2.2 |
| **Systolic Function** | | |
| EF Biplane (%) | 58 ± 5 | 60 ± 5 |

IVSd, interventricular septum thickness in diastole; LVPWd, left ventricle posterior wall thickness in diastole; LVM, left ventricle mass; LVMI, left ventricle mass index; EA-ratio, E-wave:A-wave; MV E, mitral E-wave; MV A, mitral A-wave; EdecT, E-wave deceleration time; Ee'-ratio, E-wave:mean e'; EF, ejection fraction.

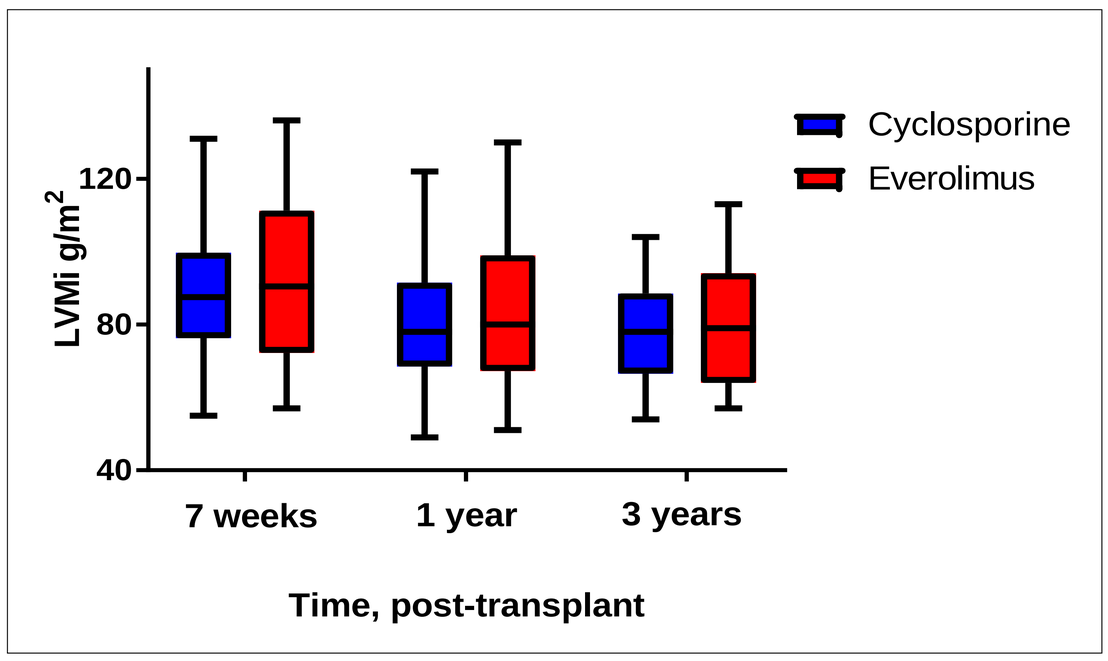
**Table 1. Baseline characteristics**

| | Everolimus (n = 38) | Cyclosporine (n = 45) |
|---|---|---|
| Age (yrs) | 51 ± 13 | 52 ± 12 |
| Male sex (%) | 73 | 74 |
| Systolic blood pressure (mmHg) | 136 ± 16 | 135 ± 14 |
| Diastolic blood pressure (mmHg) | 80 ± 12 | 82 ± 9 |
| Heart rate (bpm) | 89 ± 10 | 84 ± 11 |
| Body mass index (kg/m²) | 24 ± 4 | 25 ± 3 |
| Creatinine (µmol/l) | 111 ± 45 | 103 ± 32 |
| Glomerular filtration rate (ml/min) | 62 ± 17 | 62 ± 15 |
| Age of donor (yrs) | 41 ± 14 | 47 ± 13 |
| Male sex of donor (%) | 57 | 66 |
| Cold ischemia time (min) | 193 ± 72 | 193 ± 78 |

## RESULTS

Among the 115 patients in the SCHEDULE trial, complete data for the calculation of LVM index was available in 83 patients at 7 weeks, 82 at 1 year and 53 after 3 years. Patient demographics and echocardiography at baseline are shown in table 1 and 2. Overall, we did not observe any between-group difference in the change in LVM index during 3 years follow-up (Figure 2). From baseline to 1 year, there was a drop in LVM index in both groups (EVR: Δ-10 ± 18 g/m², CyA: Δ -9 ± 13 g/m², p < 0.01 for both), whereas in a subgroup of patients available at 3 years follow-up, we found a further insignificant nominal decrease in both treatment arms. (EVR: Δ-2 ± 19 g/m² , CyA: Δ-2 ± 13 g/m²). The proportion of patients with LVH fell significantly across treatment arms, from 21 % at baseline to only 3 % at 3 years, with no between-group difference. There were no between-group differences in LV ejection fraction or LV diastolic function during follow-up.

**Figure 2. LVM index at baseline, 1 year and 3 years follow-up**




*Box plots (median, 25 and 75 percentiles) illustrating no between-group differences in the change in LVM index during 3 years follow-up (p = 0.91 by mixed models).*

## CONCLUSION

In de novo HTX, LVM index and LVH fell significantly during 3 years follow-up, irrespective of immunosuppressive treatment.

Conflict of interest: none

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UiO : University of Oslo