Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): a randomised, multicentre, blinded, sham-controlled trial

Placement of an interatrial shunt device reduces pulmonary capillary wedge pressure during exercise in patients with heart failure and preserved or mildly reduced ejection fraction. We aimed to investigate whether an interatrial shunt can reduce heart failure events or improve health status in these patients.

Procedures

All a ien , nde en ech ca di g a h and in a i e e e ci e haem d namic e ing bef e and mi a i n c n m he had an ejec i n f ac i n f a lea 40%, he diagn i f hea fail e (eak e e ci e PCWP f a lea 25 mm Hg), and ab ence f clinicall igni can igh en ic la d f nc i n lm na a c la di ea e, a de c ibed e i l .[8] Ech ca di g am and in a i e haem d namic e e acing e e in e ed b inde enden c e lab a ie . The In e A ial Sh n De ice S em II (C ia Medical,

Statistical analysis

Sam le , i/e, e e calc la ed ba ed n da a f m he REDUCE LAP-HF I ial, a de c ibed e i , l .[8] A , ming a c mbined ca di a c la m ali and n nfa al i chaemic , ke a e f 5 0% in each ea men g a 12 m n h ; a e e , n- ea a e f hea fail e e en , f 0 39 in he , h n de ice g and 0 5 in he c n l g ; and a mean im emen in KCCQ e all , mma , c e f 13 in he , h n de ice g and eigh in he c n l g , i h an , anda d de ia i n f 20 in each ea men g , e calc la ed ha 282 e al able a ien , e ea men g ld be e , i ed f 85% e dem n a e a , igni can bene cial e ec f he a ial , h n de ice e , ham ced e a a 2- ided 0 05 le el f , igni cance , ing a Finkel ein-Sch enfeld a ach.[15] We a , med a ema e i hd a al a e f n m e han 7 5% bef e 12 m n h , e , l ing in a e , i emen en l a lea 304 and mi ed a ien , e ea men g .

Anal , i f he ima end in , all he e cac end in , , and , afe end in , a c nd c ed in he m di ed in en i n- - ea (mITT) la i n, de ned a all a ien , and ml all ca ed ecei e ea men , e cl ding h , e f nd be ineligible af e and mi a i n. In he mITT anal , i , a ien , i h mi , ing inf ma i n n ca di a c la dea h, n n-fa al i chaemic , ke, hea fail e e en , , KCCQ bef e he 12-m n h ime in , ima il d e ema e i hd a al f m he , d , e e anal , ed , ing a ailable da a. We al c nd c ed an anal , i f he e - c l la i n, de ned a a ien , h e e e al able a 12 m n h i h maj c l i la i n (a endi 32) and h e e all ca ed he , h n de ice and had an im lan e e all ca ed , ham c n l and nde en he c m le e c n l ced e.

De c i i e , a i ic f c n in , a iable e e e ed a median and IQR , . T ea men di e ence

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Results

Be een Ma 25, 2017, and J l 24, 2020, 1072 a ici an , e e en lled, 626 f h m me eligibili c i e ia f and m a , ignmen and e e a , igned ece e he a ial , h n de ice (n=314) , ham ced e (n=312; g e 1). Ba eline cha ac e i ic f a ici an , e e , imila be een , d g , (able 1; a endi 36 37), and e e ical f a ien , i h hea fail e and e ed ejec i n f ac i n (HF EF) i h hea fail e and mildl ed ced ejec i n f ac i n (HFm EF). The median age f

, , lic e, , e a 20W e e ci, e (in e ac i n=0 002). Men, a ien, i h igh a ial , l me inde in he highe, e ile (>29 7 mL/m), and a ien, i h , lm na a e , , lic e, , e a 20W f e e ci, e in he highe, e ile (>70 mm Hg) had , e hea fail, e e en , c me, i h he de ice (fa , ing , ham c n l). Ba ed n he nding f a, igni can in e ac i n e ec b ba, eline (e- and mi, a i n) , lm na a e , , lic e, , e a 20W f e e ci, e, e c nd, c ed an e l a , -h c anal, i, f addi i nal in a, i e haem d namic ma ke , , and f , nd ha he e a, a di e en ial e ec f , h, n ea men n hea fail, e e en, and KCCQ , e all , , mma , c e ba, ed n eak e e ci, e PVR. Pa ien, i h a eak e e ci, e PVR f le, han 1 74 W d , ni, (n=382) a ea ed bene f m he , h, n (in a i 1 28, =0 032; inciden a e a i f hea fail, e e en, 0 71 [95% CI 0 42 1 20]; change in laceb -c ec ed KCCQ , e all , , mma , c e 5 5 [1 6 9 5]; a endi 47 48), he ea, a ien, i h a eak e e ci, e PVR f a lea, 1 74 W d , ni, (n=188) a ea ed d , e i h he , h, n de ice (inciden a e a i f hea fail, e e en, 2 48 [1 23 5 01]; change in laceb -c ec ed KCCQ , e all , , mma , c e 6 2 [11 8 0 7], in e ac i n=0 031).

The e e e n di e ence in he c m , i e , afe end in be een he g , , (able 2). H e e, a ien, ea ed i h he, h, n e e m e likel ha e a maj ca diac e en (ca diac dea h, m ca dial infa c i n, ca diac am nade, eme genc ca diac , , ge) in he 12 m n h, af e he inde ced, e han e e a ien, h , nde en he, ham ced, e (4% vs 1%, =0 025). F, ll de ail, a e , ided in he a endi (33 34). The e e e al m e , a, c, la c m lica i n in he , h, n de ice ea men g , (18 e en , in 13 a ien , , eigh [61%] f h m had acce , , i e haema ma) han in he, ham ced, e g , (0 e en , ; a endi 43).

Discussion

O e all, am ng a ien, i h hea fail, e, an ejec i n f ac i n f a lea 40%, and d c, men ed in a, i e e e ci, e PCWP f a lea 25 mm Hg, e f , nd n , igni can di e ence be een a ial , h, n de ice ea men and, ham ced, e in e m, fca di , a, c, la dea h, n nfa al i, chaemic , ke, al a e f , ening hea fail, e e en , , and heal h , a , . H e e, he e e e di e en ial ea men e ec, in , me f he e, eci ed , , bg , , . Men and a ien, i h , lm na a e , , lic e, , e fa lea 70W a 20W f e e ci, e igh a ial , l me inde f a lea 29 7 mL/m a ea ed ha e m e fe, , en hea fail, e e en, i h he de ice. F, he , -h c anal, e, e ealed ha a ien, i h a eak e e ci, e PVR f le, han 1 74 W d , ni, (hich c e, nd he , e limi f n mal) migh e e, en a e, nde g , , i h im , ed , c me and heal h , a , , i h a ial , h, n de ice ea men c m a ed i h , ham c n l. The , e all c m , i e , afe end in a , imila be een ea men g , , , al h , gh, h, n de ice- ea ed a ien, had a highe f e, , enc f , a, c, la c m lica i n and maj ca diac e en, han, ham- ea ed a ien, .

The REDUCE LAP-HF II ial a, de, igned n he ba, i, f he , i, i e e, , l, f he REDUCE LAP-HF I ial, hich, h ed ha he C , ia a ial, h, n de ice a a, cia ed i h a ed, c i n in e e ci, e PCWP a 1 m n h af e and mi, a i n c m a ed i h , ham c n l, c n ming i, mechani, ic bene in a ien, i h HF EF HFm EF.[7] In addi i n, he le el f PCWP ed, c i n in he, h, n de ice- ea ed a ien, in he REDUCE LAP-HF I ial, h , gh m de , (eg, 5 0 mm Hg mean dec ea, e i h leg , ; 3 2 mm Hg dec ea, e a 20W e e ci, e a 1 m n h af e de ice im lan a i n) i, likel be clinicall meaningf, l

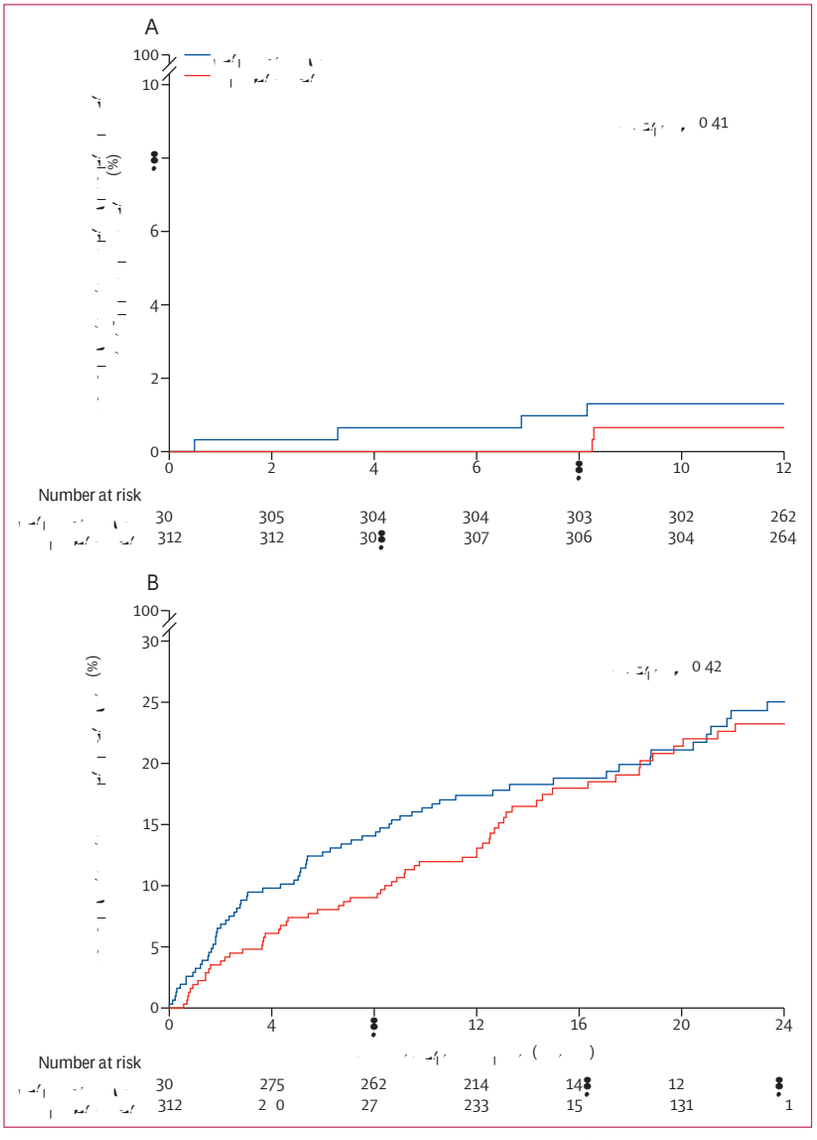

Figure 2: Kaplan-Meier estimates of primary e□cacy outcomes among heart failure with ejection fraction of at least 40% randomly allocated to the atrial shunt device versus sham procedure
(A) Cardiovascular death or non-fatal ischaemic stroke. (B) Heart failure events requiring treatment.

Figure 3: Forest plot of treatment effect on recurrent heart failure events by prespecified subgroups
All prespecified echocardiographic and invasive haemodynamic subgroups are shown in the appendix (p 46). NYHA=New York Heart Association. HFmrEF=heart

(a endi 49), ba ed n he a , cia i n be een l e
al e f leg , and e e ci e PCWP i h l e i k f
hea fail e e en , . H e e , e cann e ha
, h n de ice-a , cia ed l e ing f e e inal PCWP i
a , cia ed i h im ed , c me ba ed n he de ign
f he e en ial, hich did n incl de , e ial
haem d namic e ing.

The REDUCE LAP-HF II ial e , ied each a ien
nde g in a i e e e ci e haem d namic e ing
c n m he diagn , i f hea fail e in he e ence f
ejec i n f ac i n f a lea 40%, hich added c n ide able
ig he ial. Ne e hele , , e en in acc a el
diagn , ed a ien , , HF EF and HFm EF can be
a , cia ed i h m l i le a ing ae i l gie and
a h h , i l gie, ha nde l i, he e genei .[18] T be
bene cial, in e a ial , h n ing e , i e a , eci c
hen e: ele a ed lef a ial e , e in he ab ence f
igh -, ided hea fail e , igni can lm na a c la
di ea e. Indeed, REDUCE LAP-HF II and e i , ial
f he C ia A ial Sh n in e , ence ha e all been
en ichmen ial, a e f eci i n medicine ial,[19,20]
i h each d c men ing ele a ed e e ci e PCWP (a
, ga e f lef a ial e , e) and , ing c m ehen i e
n n-in a i e and in a i e diagn , ic , elec a ien ,
h e e m , likel bene f m he, h n .

The e , l , f REDUCE LAP-HF II highligh a
en iall im an e cl , i n c i e i n f in e a ial
, h n de ice ea men lm na a c la di ea e
nc e ed d ing e e ci e. T e ic en lmen
indi id al e ec ed bene f m , h n de ice
ea men , e e cl ded a ien , i h e ing indica ,
f igh hea fail e and lm na a c la di ea e
(incl ding , igni can igh en ic la d , f nc i n,
igh a ial e , e >14 mm Hg, and PVR >3 5 W d
ni ,). H e e , , a eg migh ha e been
inade a e f e cl ding lm na a c la di ea e
nc e ed b e e ci e, , ince ea men i h he , h n
de ice a, a , cia ed i h , e c me in a ien ,
i h eak e e ci e PVR f a lea 1 74 W d ni , ,
he ea he e a, a , gge i n f a en ial bene cial
e n e , h n de ice he a in a ien , i h a
n mal lm na a c la e n e e e ci e. The
ea n f he e di e en ial c me e , i e f he
im e iga i n. I i kn n ha man a ien , i h
HF EF di la ele a i n in PVR d ing e e ci e ha
a e n a a en a e , hich inc ea e af e l ad n he
igh en icle, he eb e , l ing in inc ea ed igh a ial
e , e,[21] en iall leading m e f e , en hea
fail e e en , and , e heal h , a , . Thi hen -
men n migh al im ai igh -, ided en ic la -a e ial
c ling and f he c n ib e igh en ic la
fail e.[22] T ea men i h a ial , h n de ice in a ien ,
i h e idence f lm na a c la di ea e d ing
e e ci e c ld al accele a e de el men f igh
en ic la d , f nc i n, hich i , ngl a , cia ed
i h inc ea ed m bidi and m ali in HF EF.[23,24]
The a a en , e di e ence in e n e , h n de ice
ea men al e , i e f he im e iga i n. Men ha e
la ge igh a ial l me and , e igh en ic la
, , lic f nc i n han men, b h f hich c ld ha e
led , e c me i h , h n de ice ea men .
Inc ea ed igh a ial l me, hich e e al a , cia ed
i h , e c me i h he de ice, c ld be indica i e
f g ea e ch nic e l ad f he igh hea hich
c ld ha e ham e ed lef a ial dec m e , i n ia
he , h n de ice and , bclinical igh en ic la
d , f nc i n hich migh ha e e, nded nfa abl
lef - - igh , h n ing.

Al h gh e i , and mi ed ial f angi en, in

ra, c- la c m lica i n,) and maj ca diac e en , , h - gh ela i el a e, e e m e c mm n in , h- n de ice- ea ed a ien , , he e en ial ad e , e e ec , m- , be eighed again, an en ial bene , f lef - - igh , h- n ing in , - bg - , f a ien , i h HF EF and HFm EF h migh e nd fa - abl he a ial , h- n de ice.

Se e al limi a i n, , h - ld be c n ide ed hen in e eing he ial e , - l , . Al h - gh ba ed n e- , eci ed , - bg - anal , e dem n, a ing a di e en ial ea men e ec b e ence ab ence f , igni can l ele a ed - lm na a e , , lic e , - e d- ing e e ci e, he eak e e ci e PVR , - bg - anal , e, e e d ne , h c and h- , , h - ld be c n ide ed e l a . The e a, a la ge im - emen in he KCCQ , c e in he c n l g - , hich migh ha e made i di c l , h a bene in heal h , a - , i h he de ice. H e e, ecen hea fail- e ial, ha e, h n ha ba, eline KCCQ , c e i, im e , el ela ed im - emen in KCCQ , c e in he c n l g - (a endi 44, 50); he ef e, i i, n , - i ing ha he e a, a la ge im - emen in he c n l g - in he e en ial, gi en he - e l KCCQ , c e, a ba, eline. The b, e - ed m ali a e in he ial a, m- ch l e han he edic ed m ali a e. H e e, a ien , i h maj i k fac , f inc ea ed m ali in HF EF and HFm EF (, - ch a , igni can igh - en ic- la d , f- nc i n, - e - lm na - a, c- la di ea, e, and inabili e e ci e) e e e cl- ded, hich c - ld ha e led he l e - han-e ec ed m ali a e. Al h - gh he l ng- e m e cac and , afe f he a ial , h- n de ice c m a ed i h , ham c n l cann e be e ed, he e i - , en-label (n=64) and REDUCE LAP-HF I and mi ed clinical ial, (n=44) ha e dem n a ed e cellen l ng- e m d- abili and , afe f he de ice, and all a ien , in he ial ill be f ll ed - f a lea, 5 ea , . O- e , - l , al, nl a l he 8-mm , h- n diame e f he C - ia A ial Sh- n De ice. Whe he , imila e , - l , - ld cc- i h , malle la ge in e a ial , h- n , emain be de e mined. I i al , , ible ha a ien , i h a ical f m, f hea fail- e i h ejec i n fac i n f a lea 40% (eg, in l a i e ca di m a h) e e inad e en l en lled in he ial, h - gh - nlikel gi en he e - - i emen , f a e, e - ed ca diac inde and a di e ence be een PCWP and igh a ial e , - e f a lea 5 mm Hg. Finall , COVID-19 a a , cia ed i h a l e hea fail- e e en a e d- ing f ll - , an b, e - a i n hich ha been ell d c- men ed in a ien , i h hea fail- e in he COVID-19 e a.[28,29] H e e, he l e hea fail- e e en a e did n a ea ha e a , igni can e ec n he ima - c me, and he - e all a e f hea fail- e e en , (de, i e COVID) a, m e han ice a high a, ecen HF EF ha mac he a ial, .[26,30]

In , - mma , in hi ade- - a el e ed, , ham- c n lled, and mi ed ial f a ien , i h hea fail- e and ejec i n fac i n f a lea 40%, lacemen f an a ial , h- n de ice did n e, - l in a ed- c i n in al a e f hea fail- e e en , im - emen in heal h , a - , . H e e, ea men e cac di e ed b e ence ab ence f - lm na - a, c- la di ea, e - nma ked b e e ci e; a ien , i h n e idence f - lm na - a, c- la di ea, e d- ing e e ci e a ea ed bene f m he de ice he ea a ien , i h ele a ed PVR d ing e e ci e had , e - c me, . Addi i nal , - die ill be e , - i ed e al- a e he e cac , , afe , d- abili , and l ng- e m clinical im ac f a ial , h- n de ice ea men in a ien , i h hea fail- e and ejec i n fac i n f a lea 40% i h n e idence f - lm na - a, c- la di ea, e d- ing e e ci e.

Contributors

SJS, MBL, DEC, JMM, SDS, and DJ V de igned he , - d . SJS, BAB, ESC, PD, PSF, GH, RK, DMK, SEL, PL, RCM, MJR, ALS, VS, and SW c llec ed a ien da a. All a- h , anal , ed and in e e ed he da a. QG and JMM e e he inde enden , - d bi , a i ician e n ible f he, a i ical anal , e . SJS e he , d af f he e . All a- h , a ici a ed in he i ing f he e , ag eed n he c n en f he man- , c i , e ie ed d af , and a - ed he nal - e , i n. SJS, DEC, QG, and JMM had - n e ic ed acce , and - e i ed he - nde l ing da a. S a i ical anal , e e e c nd- c ed inde enden l b QG and JMM. All a- h , had f- ll e n ibili f he deci i n - bmi f - blica i n.

Declaration of interests

SJS e , e ea ch g an , f m he Na i nal In i e f Heal h (NIH; U54 HL160273, R01 HL107577, R01 HL127028, R01 HL140731, and R01 HL149423), Ac eli n, A aZeneca, C - ia, N - a i , and P e ; and e nal fee f m Abb , Ac eli n, A aZeneca, Amgen, A ia CV, A n The a ie , Ba e , B eh inge -Ingelheim, B , n Scien i c, B i l M e , S- - ibb, Ca di a, C idea, CVR , C cle i n, C kine ic , Ed a d Life cience , Eid , , Ei ai, Ima a, Im - l e D namic , In ellia, I ni , I n d, Lill , Me ck, M Ka dia, N - a i , N - N di k, P e , P hena, Regene n, Ri - , , San , Shifamed, Tena , Tena a, and Uni ed The a e ic . BAB e , e ea ch f- nding f m he Na i nal In i e f Heal h, A n, A aZeneca, C - ia, Med nic, Gla Smi hKline, Me bla , N - a i , and Tena The a e ic ; and e nal fee f m Ac eli n, Amgen, A ia, B eh inge Ingelheim, Ed a d , Eli Lill , Imb ia, Jan , en, Me ck, N - N di k, and VAD - a i n . ESC e , e . nal fee f m Abb , EBR , em , Med nic, In e , h n, Li aN - a, CVR , and Ca di n mic . GH e , e . nal fee f m A aZeneca, Ba e , B eh inge Ingelheim, Im - l e D namic , N - a i , P e , Se - ie , and Vif Pha ma. RK e , e . nal fee f m Med nic, Im - l e D namic , and Ca di n mic. SEL e , e . nal fee f m A n The a ie and CVR . PL e , e ea ch g an , f m Abb Va, c- la , Ed a d Life cience , and ReC . JMM e , e . nal fee f m C - ia. RCM e , e . nal fee f m P e , Akcea, Eid , , Aln lam, and Ca eD . SDS e , e ea ch g an , f m Ac eli n, Aln lam, Amgen, A aZeneca, Belle h n, Ba e , B i l M e S- - ibb, Cellad n, C kine ic , Eid , , Gilead, Gla Smi hKline, I ni , Lill , Me bla , M Ka dia, NIH, Ne nik, N - a i , N - N di k, Re ica dia, San Pa e , The ac , , and US2.AI; and e nal fee f m Abb , Ac in, Ak , , Aln lam, Amgen, A ena, A aZeneca, Ba e , B e inge Ingelheim, B i l M e, S- - ibb, Ca di , Ca d- in, C - ia, C kine ic , Daiichi-Sank , Gla Smi hKline, Lill , Me ck, M ka dia, N - a i , R che, The ac , , Q- an - m Gen mic , Ca d- in, Jan , en, Ca diac Dimen in , Tena a, San -Pa e , Dina - , T emea - , CellP The a, M de na, Ame ican Regen , Sa e a, Le ic n, Anaca di , Ak , , P eHeal h. ALS e , e ea ch g an , f m he Na i nal Hea F - nda i n fA , alia F - e Leade Fell , hi , (#101918 & 106025), NSW Heal h (A , alia), Bi nik, RACE Onc l g , B i l M e S- - ibb, R che Diagn , ic , and Vif ; and e nal fee f m N - a i , Ba e , B i l M e S- - ibb, A aZeneca, and B eh inge Ingelheim. VS e , e , nal fee f m Abb Lab a ie and B , n Scien i c. SW e , e , nal fee f m N - a i , A aZeneca, and Ba e . MBL e , in i - inal e ea ch g an , f m Abb , B , n Scien i c, Ed a d LifeScience , and Med nic. he i, Lie , .

38137–60.

Data sharing

Da a e. . e. . can be . bmi ed C ia Medical (inf @c iamedical.c m). Da a ill be . ha ed i h e. ea che . h . bmi a de ailed e. ea ch . al n a al b he . d . ee ing c mmi ee. Da a ill n be made a ailable n il af e a al f he d c in he USA and Ja an and n n il e ing f he nal e. l . a e c ed in 2027. Indi id al a ien da a ill be . ha ed in da a. e . in a de-iden i ed and an n mi. ed f ma .

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