Once-Daily 2-Drug versus 3-Drug Antiretroviral Therapy for HIV Infection in Treatment-naive Adults: Less Is Best?

Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet. 2019;393:143-155.

Study Overview

Objective. To evaluate the efficacy and safety of a once-daily 2-drug antiretroviral (ARV) regimen, dolutegravir plus lamivudine, for the treatment of HIV-1 infection in adults naive to antiretroviral therapy (ART).

Design. GEMINI-1 and GEMINI-2 were 2 identically designed multicenter, double-blind, randomized, noninferiority, phase 3 clinical trials conducted between July 18, 2016 and March 31, 2017. Participants were stratified to receive 1 of 2 once-daily HIV regimens: the study regimen, consisting of once-daily dolutegravir 50 mg plus lamivudine 300 mg, or the standard-of-care regimen, consisting of once-daily dolutegravir 50 mg plus tenofovir disoproxil fumarate (TDF) 300 mg plus emtricitabine 200 mg. While this article presents results at week 48, both trials are scheduled to evaluate participants up to week 148 in an attempt to evaluate long-term efficacy and safety.

Setting and participants. Eligible participants had to be aged 18 years or older with treatment-naive HIV-1 infection. Women were eligible if they were not (1) pregnant, (2) lactating, or (3) of reproductive potential, defined by various means, including tubal ligation, hysterectomy, postmenopausal, and the use of highly effective contraception. Initially, eligibility screening restricted participation to those with viral loads between 1000 and 100,000 copies/mL. However, the upper limit was later increased to 500,000 copies/mL based on an independent review of results from other clinical trials[1,2] evaluating dual therapy with dolutegravir and lamivudine, which indicated efficacy in patients with viral loads up to 500,000.[3-5]

Notable exclusion criteria included: (1) major mutations to nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors; (2) evidence of hepatitis B infection; (3) hepatitis C infection with anticipation of initiating treatment within 48 weeks of study enrollment; and (4) stage 3 HIV disease, per Centers for Disease Control and Prevention criteria, with the exception of cutaneous Kaposi sarcoma and CD4 cell counts < 200 cells/mL.

Main outcome measures. The primary endpoint was demonstration of noninferiority of the 2-drug ARV

regimen through assessment of the proportion of participants who achieved virologic suppression at week 48 in the intent-to-treat-exposed population. For the purposes of this study, virologic suppression was defined as having fewer than 50 copies of HIV-1 RNA per mL at week 48. For evaluation of safety and toxicity concerns, renal and bone biomarkers were assessed at study entry and at weeks 24 and 48. In addition, participants who met virological withdrawal criteria were evaluated for integrase strand transfer inhibitor mutations. Virological withdrawal was defined as the presence of 1 of the following: (1) HIV RNA > 200 copies/mL at week 24, (2) HIV RNA > 200 copies/mL after previous HIV RNA < 200 copies/mL (confirmed rebound), and (3) a < 1 $\log_{10}$ copies/mL decrease from baseline (unless already < 200 copies/mL).

Main results. GEMINI-1 and GEMINI-2 randomized a combined total of 1441 participants to receive either the once-daily 2-drug ARV regimen (dolutegravir and lamivudine, *n* = 719) or the once-daily 3-drug ARV regimen (dolutegravir, TDF, and emtricitabine, *n* = 722). Of the 533 participants who did not meet inclusion criteria, the predominant reasons for exclusion were either having preexisting major viral resistance mutations (*n* = 246) or viral loads outside the range of 1000 to 500,000 copies/mL (*n* = 133).

Baseline demographic and clinical characteristics were similar between both groups. The median age was 33 years (10% were over 50 years of age), and participants were mostly male (85%) and white (68%). Baseline HIV RNA counts of > 100,000 copies/mL were found in 293 participants (20%), and 188 (8%) participants had CD4 counts of ≤ 200 cells/mL.

Noninferiority of the once-daily 2-drug versus the once-daily 3-drug ARV regimen was demonstrated in both the GEMINI-1 and GEMINI-2 trials for the intent-to-treat-exposed population. In GEMINI-1, 90% (*n* = 320) in the 2-drug ARV group achieved virologic suppression at week 48 compared to 93% (*n* = 332) in the 3-drug ARV group (no statistically significant difference). In GEMINI-2, 93% (*n* =335) in the 2-drug ARV group achieved virologic suppression at week 48 compared to 94% (*n* = 337) in the 3-drug ARV group (no statistically significant difference).

A subgroup analysis found no significant impact of baseline HIV RNA (> 100,000 compared to ≤ 100,000 copies/mL) on achieving virologic suppression at week 48. However, a subgroup analysis did find that participants with CD4 counts < 200 copies/mL had a reduced response in the once-daily 2-drug versus 3-drug ARV regimen for achieving virologic response at week 48 (79% versus 93%, respectively).

Overall, 10 participants met virological withdrawal criteria during the study period, and 4 of these were on the 2-drug ARV regimen. For these 10 participants, genotypic testing did not find emergence of resistance to either nucleoside reverse transcriptase or integrase strand transfer inhibitors.

Regarding renal biomarkers, increases of both serum creatinine and urinary excretion of protein creatinine were significantly greater in the 3-drug ARV group. Also, biomarkers indicating increased bone turnover were elevated in both groups, but the degree of elevation was significantly lower in the 2-drug ARV regimen cohort. It is unclear whether these findings reflect an increased or decreased risk of developing osteopenia or osteoporosis in the 2 study groups.

Conclusion. The once-daily 2-drug ARV regimen dolutegravir and lamivudine is noninferior to the guideline-recommended once-daily 3-drug ARV regimen dolutegravir, TDF, and emtricitabine at achieving viral suppression in ART-naive HIV-1 infected individuals with HIV RNA counts < 500,000 copies/mL. However, the efficacy of this ARV regimen may be compromised in individuals with CD4 counts < 200 cells/mL.

Commentary

Currently, the mainstay of HIV pharmacotherapy is a 3-drug regimen consisting of 2 nucleoside reverse transcriptase inhibitors in combination with 1 drug from another class, with an integrase strand transfer inhibitor being the preferred third drug.[6] Despite the improved tolerability of contemporary ARVs, there remains concern among HIV practitioners regarding potential toxicities associated with cumulative drug exposure, specifically related to nucleoside reverse transcriptase inhibitors. As a result, there has been much interest in evaluating 2-drug

ARV regimens for HIV treatment in order to reduce overall drug exposure.[7-10]

The 48-week results of the GEMINI-1 and GEMINI-2 trials, published in early 2019, further expand our understanding regarding the efficacy and safety of 2-drug regimens in HIV treatment. These identically designed studies evaluated once-daily dolutegravir and lamivudine for HIV in a treatment-naive population. This goes a step further than the SWORD-1 and SWORD-2 trials, which evaluated once-daily dolutegravir and rilpivirine as a step-down therapy for virologically suppressed individuals and led to the U.S. Food and Drug Administration (FDA) approval of the single-tablet combination regimen dolutegravir/rilpivirine (Juluca).[10] Therefore, whereas the SWORD trials evaluated a 2-drug regimen for maintenance of virologic suppression, the GEMINI trials assessed whether a 2-drug regimen can both achieve and maintain virologic suppression.

The results of the GEMINI trials are promising for a future direction in HIV care. The rates of virologic suppression achieved in these trials are comparable to those seen in the SWORD trials.[10] Furthermore, the virologic response seen in the GEMINI trials is comparable to that seen in similar trials that evaluated a 3-drug ARV regimen consisting of an integrase strand transfer inhibitor–based backbone in ART-naive individuals.[11,12]

A major confounder to the design of this trial was that it included TDF as one of the components in the comparator arm, an agent that has already been demonstrated to have detrimental effects on both renal and bone health.[13,14] Additionally, the bone biomarker results were inconclusive, and the agents' effects on bone would have been better demonstrated through bone mineral density testing, as had been done in prior trials.

Applications for Clinical Practice

Given the recent FDA approval of the single-tablet combination regimen dolutegravir and lamivudine (Dovato), this once-daily 2-drug ARV regimen will begin making its way into clinical practice for certain patients. Prior to starting this regimen, hepatitis B infection first must be ruled out due to poor efficacy of lamivudine monotherapy for management of chronic hepatitis B infection.[15] Additionally, baseline genotype testing should be performed prior to starting this ART given that approximately 10% of newly diagnosed HIV patients have baseline resistance mutations.[16] Obtaining rapid genotype testing may be difficult to accomplish in low-resource settings where such testing is not readily available. Finally, this approach may not be applicable to those presenting with acute HIV infection, in whom viral loads are often in the millions of copies per mL. It is likely that dolutegravir/lamivudine could assume a role similar to that of dolutegravir/rilpivirine, in which patients who present with acute HIV step down to a 2-drug regimen once their viral loads have either dropped below 500,000 copies/mL or have already been suppressed.

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Use of Hybrid Coronary Revascularization in Patients with Multivessel Coronary Artery Disease

Tajstra M, Hrapkowicz T, Hawranek M, et al. Hybrid coronary revascularization in selected patients with multivessel disease. JACC Cardiovascular Interventions. 2018;11:847-852.

Study Overview

Objective. To investigate the 5-year clinical outcome of patients undergoing hybrid revascularization for multivessel coronary artery disease (CAD).

Design. Multicenter, open-label, prospective randomized control trial.

Setting and participants. 200 patients with multivessel CAD referred for conventional surgical revascularization were randomly assigned to undergo hybrid coronary revascularization (HCR) or coronary artery bypass grafting (CABG).

Main outcome measures. The primary endpoint was all-cause mortality at 5 years.

Main results. After excluding 9 patients who were lost to follow-up before 5 years, 191 patients (94 in HCR group and 97 in CABG group) formed the basis of the study. All-cause mortality at 5-year follow-up was similar in the 2 groups (6.4% versus 9.2%, $P = 0.69$). The rates of myocardial infarction (4.3% versus 7.2%, $P = 0.30$), repeat revascularization (37.2% versus 45.4%, $P = 0.38$), stroke (2.1% versus 4.1%, $P = 0.35$), and major adverse and cardiac and cerebrovascular events (45.2% versus 53.4%, $P = 0.39$) were similar in the 2 groups. These findings were consistent across all levels of risk for surgical complications (EuroScore) and for complexity of revascularization (SYNTAX score).

Conclusion. HCR has similar 5-year all-cause mortality when compared with conventional CABG.

Commentary

HCR has been proposed as a less invasive, effective alternative revascularization strategy to conventional CABG for patients with multivessel CAD. The hybrid approach typically combines the long-term durability of grafting of the left anterior descending artery (LAD) using the left in-

ternal mammary artery and the percutaneous coronary intervention (PCI) for non-LAD stenosis; this approach has been shown to have similar or perhaps even better long-term patency compared with saphenous vein grafts.[1,2] Previous studies have demonstrated the feasibility of HCR by comparing HCR to conventional CABG at 1 year.[2] However, the long-term outcome of HCR compared to conventional CABG has not been previously reported.

In this context, Tajstra et al reported the 5-year follow-up from their prospective randomized pilot study. They report that among the 200 patients with multivessel coronary disease randomly assigned to either HCR or CABG, all-cause mortality at 5-year follow-up was similar in the 2 groups (6.4% versus 9.2%, $P = 0.69$). The rates of myocardial infarction, repeat revascularization, stroke, and major adverse and cardiac and cerebrovascular event (MACCE) were also similar in the 2 groups.

This is an important study because it is the first to compare the long-term outcome of HCR with conventional CABG; previous studies have been limited due to their short- to mid-term follow-up.[2] However, because this study was not powered to assess the superiority of the HCR compared to conventional CABG, future randomized control trials with a larger number of patients are needed.

Future studies must address some important questions. First, the patients in the present study were younger (mean age, 62.1 ± 8.3 years) with less comorbidity and a relatively low SYNTAX score (23.6 ± 6.1 for the HCR arm). As CABG and PCI are associated with similar long-term outcomes in patients with low (< 22) to intermediate (22–32) SYNTAX score,[3] comparisons between HCR and multivessel PCI using the current generation of drug-eluting stents are needed. The results from the ongoing Hybrid Coronary Revascularization Trial (NCT03089398) will shed light on this clinical question. Second, whether these findings can be extended to patients with a high baseline SYNTAX score needs further study. Nonetheless, outcomes were similar between the 2 strategies in the intermediate ($n = 98$) and high ($n = 8$) SYNTAX score groups. Interestingly, there is no clear benefit of HCR in the high surgical risk groups as measured by EuroScore. Third, in addition to the hard outcomes (death and MACCE), the quality of life of patients measured by an established metric, such as the Seattle Angina Questionnaire, need to be assessed. Last, the completeness of revascularization in each group needs to be further evaluated because incomplete revascularization is a known predictor of adverse outcomes.[4,5]

Applications for Clinical Practice

In patients with multivessel coronary disease with low SYNTAX score, the 5-year outcome for HCR was similar to that of conventional CABG. Further larger studies are needed to assess the superiority of this approach.

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Does Vitamin D Supplementation Improve Lower Extremity Power and Function in Community-Dwelling Older Adults?

Shea MK, Fielding RA, Dawson-Hughes B. The effect of vitamin D supplementation on lower-extremity power and function in older adults: a randomized controlled trial. Am J Clin Nutr. 2019;109:369-379.

Study Overview

Objective. To test the effect of 12 months of vitamin D supplementation on lower-extremity power and function in older community-dwelling adults screened for low serum 25-hydroxyvitamin D (25(OH)D).

Design. A single-center, double-blind, randomized placebo-controlled study in which participants were assigned to 800 IU of vitamin D_3 supplementation or placebo daily and were followed over a total period of 12 months.

Setting and participants. A total of 100 community-dwelling men and women aged ≥ 60 years with serum 25(OH)D ≤ 20 ng/mL at screening participated. Participants were prescreened by phone, and were excluded if they met any of the following exclusion criteria: vitamin D supplement use > 600 IU/day (for age 60-70 years) or > 800 IU/day (for age ≥ 71 years); vitamin D injection within the previous 3 months; > 2 falls or 1 fall with injury in past year; use of cane, walker, or other indoor walking aid; history of kidney stones within past 3 years; hypercalcemia (serum calcium > 10.8 mg/dL); renal dysfunction (glomerular filtration rate, < 30 mL/min); history of liver disease, sarcoidosis, lymphoma, dysphagia, or other gastrointestinal disorder; neuromuscular disorder affecting lower-extremity function; hip replacement within the past year; cancer treatment in the past 3 years; treatment with thiazide diuretics > 37.5 mg, teriparatide, denosumab, or bisphosphonates within the past 2 years; oral steroids (for > 3 weeks in the past 6 months); and use of fat malabsorption products or anticonvulsive therapy.

Main outcome measures. The primary outcome was leg extensor power assessed using a computer-interfaced bilateral Keiser pneumatic leg press. Secondary outcomes to measure physical function included: (1) backward tandem walk test (which is an indicator of balance and postural control during movement[1]); (2) Short Physical Performance Battery (SPPB) testing, which includes a balance assessment (ability to stand with feet positioned normally, semi-tandem, and tandem for 10s), a timed 4-m walk, and a chair stand test (time to complete 5 repeated chair stands); (3) stair climbing (ie, time to climb 10 steps, as a measure of knee extensor strength and functional capacity); and (4) handgrip strength (using a dynamometer). Lean tissue mass was assessed by dual X-ray absorptiometry (DEXA scan). Finally, other measures included serum total 25(OH)D levels measured at baseline, 4, 8, and 12 months, as well as 24-hour urine collection for urea-nitrogen and creatinine measurements.

Main results. Of the 2289 individuals screened for the study, 100 met eligibility criteria and underwent randomization to receive either 800 IU vitamin D supplementation daily (n = 49) or placebo (n = 51). Three patients (2 in vitamin D group and 1 in placebo group) were lost to follow up. The mean age of all participants was 69.6 ± 6.9 years. In the vitamin D group versus the control group, respectively, the percent male: female ratio was 66:34 versus 63:37, and percent Caucasian was 75% versus 82%. Mean body mass index was 28.2 ± 7.0 and mean serum 25(OH)D was 20.2 ± 6.7 ng/mL. At the end of the study (12 months), 70% of participants given vitamin D supplementation had 25(OH)D levels ≥ 30 ng/mL and all participants had levels ≥ 20 ng/mL. In the placebo group, the serum 25(OH)D level was ≥ 20 ng/mL in 54% and ≥ 30 ng/mL in 6%. The mean serum 25(OH)D level increased to 32.5 ± 5.1 ng/mL in the vitamin D–supplemented group,

but no significant change was found in the placebo group (treatment × time, $P < 0.001$). Overall, the serum 1,25 (OH)2D3 levels did not differ between the 2 groups over the intervention period (time, $P = 0.49$; treatment × time, $P = 0.27$). Dietary intake of vitamin D, calcium, nitrogen, and protein did not differ or change over time between the 2 groups. The change in leg press power, function, and strength did not differ between the groups over 12 months (all treatment × time, P values ≥ 0.60). A total of 27 falls were reported (14 in vitamin D versus 9 in control group), of which 9 were associated with injuries. There was no significant change in lean body mass at the end of the study period in either group (treatment × time, $P = 0.98$).

Conclusion. In community-dwelling older adults with vitamin D deficiency (≤ 20 ng/mL), 12-month daily supplementation with 800 IU of vitamin D_3 resulted in sufficient increases in serum 25(OH)D levels, but did not improve lower-extremity power, strength, or lean mass.

Commentary

Vitamin D deficiency is common in older adults (prevalence of about 41% in US adults ≥ 65 years old, according to Forrest et al[2]) and is likely due to dietary deficiency, reduced sun exposure (lifestyle), and decreased intestinal calcium absorption. As such, vitamin D deficiency has historically been a topic of debate and of interest in geriatric medicine, as it relates to muscle weakness, which in turn leads to increased susceptibility to falls.[3] Interestingly, vitamin D receptors are expressed in human skeletal muscle,[4] and in one study, 3-month supplementation of vitamin D led to an increase in type II skeletal muscle fibers in older women.[5] Similarly, results from a meta-analysis of 5 randomized controlled trials (RCTs)[6] showed that vitamin D supplementation may reduce fall risk in older adults by 22% (corrected odds ratio, 0.78; 95% confidence interval, 0.64-0.92). Thus, in keeping with this general theme of vitamin D supplementation yielding beneficial effects in clinical outcomes, clinicians have long accepted and practiced routine vitamin D supplementation in caring for older adults.

In more recent years, the role of vitamin D supplementation in primary care has become controversial,[7] as observed in a recent paradigm shift of moving away from routine supplementation for fall and fracture prevention in clinical practice.[8] In a recent meta-analysis of 33 RCTs in older community-dwelling adults, supplementation with vitamin D with or without calcium did not result in a reduction of hip fracture or total number of fractures.[9] Moreover, the United States Preventive Services Task Force (USPSTF) recently published updated recommendations on the use of vitamin D supplementation for primary prevention of fractures[10] and prevention of falls[11] in community-dwelling adults. In these updated recommendations, the USPSTF indicated that insufficient evidence exists to recommend vitamin D supplementation to prevent fractures in men and premenopausal women, and recommends against vitamin D supplementation for prevention of falls. Finally, USPSTF recommends against low-dose vitamin D (400 IU or less) supplementation for primary prevention of fractures in community-dwelling, postmenopausal women.[10] Nevertheless, these statements are not applicable for individuals with a prior history of osteoporotic fractures, increased risk of falls, or a diagnosis of vitamin D deficiency or osteoporosis. Therefore, vitamin D supplementation for prevention of fall and fractures should be practiced with caution.

Vitamin D supplementation is no longer routinely recommended for fall and fracture prevention. However, if we believe that poor lower extremity muscle strength is a risk factor for falls,[12] then the question of whether vitamin D has a beneficial role in improving lower extremity strength in older adults needs to be addressed. Results regarding the effect of vitamin D supplementation on muscle function have so far been mixed. For example, in a randomized, double-blinded, placebo-controlled trial of 160 postmenopausal women with low vitamin D level (< 20 ng/mL), vitamin D_3 supplementation at 1000 IU/day for 9 months showed a significant increase in lower extremity muscle strength.[13] However, in another randomized double-blinded, placebo-controlled trial of 130 men aged 65 to 90 years with low vitamin D level (< 30 ng/mL) and an SPPB score of ≤ 9 (mild-moderate limitation in mobility), daily supplementation with 4000 IU of vitamin D_3 for 9 months did not result in improved SPPB score or gait speed.[14] In the study reported by Shea et al, the authors showed that 800 IU of daily vitamin D supple-

mentation (consistent with the Institute of Medicine [IOM] recommendations for older adults[15]) in community-dwelling older adults with vitamin D deficiency (< 20 ng/mL) did not improve lower extremity muscle strength. This finding is significant in that it adds further evidence to support the rationale against using vitamin D supplementation for the sole purpose of improving lower extremity muscle function in older adults with vitamin D deficiency.

Valuable strengths of this study include its randomized, double-blinded, placebo-controlled trial design testing the IOM recommended dose of daily vitamin D supplementation for older adults. In addition, compared to some of the prior studies mentioned above, the study population included both males and females, although the final study population resulted in some gender bias (with male predominance). Moreover, participants were followed for a sufficient amount of time (1 year), with an excellent adherence rate (only 3 were lost to follow-up) and with corresponding improvement in vitamin D levels. Finally, the use of SPPB as a readout for primary outcome should also be commended, as this assessment is a well-validated method for measuring lower extremity function with scaled scores that predict poor outcomes.[16] However, some limitations include the aforementioned predominance of male participants and Caucasian race in both intervention and control groups, as well as discrepancies between the measurement methods for serum vitamin D levels (ie, finger-stick cards versus clinical lab measurement) that may have underestimated the actual serum 25(OH)D levels.

Applications for Clinical Practice

While the null findings from the Shea and colleagues study are applicable to healthier community-dwelling older adults, they may not be generalizable to the care of more frail older patients due to their increased risks for falls and high vulnerability to adverse outcomes. Thus, further studies that account for baseline sarcopenia, frailty, and other fall-risk factors (eg, polypharmacy) are needed to better evaluate the value of vitamin D supplementation in this most vulnerable population.

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Delayed Cardioversion Noninferior to Early Cardioversion in Recent-Onset Atrial Fibrillation

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Study Overview

Objective. To assess whether immediate restoration of sinus rhythm is necessary in hemodynamically stable, recent onset (< 36 hr), symptomatic atrial fibrillation in the emergency department.

Design. Multicenter, randomized, open-label, noninferiority trial, RACE 7 ACWAS (Rate Control versus Electrical Cardioversion Trial 7--Acute Cardioversion versus Wait and See).

Setting and participants. 15 hospitals in the Netherlands, including 3 academic hospitals, 8 nonacademic teaching hospitals, and 4 nonteaching hospitals. Patients 18 years of age or older with recent-onset (< 36 hr), symptomatic atrial fibrillation without signs of myocardial ischemia or a history of persistent atrial fibrillation who presented to the emergency department were randomized in a 1:1 ratio to either a wait-and-see approach or early cardioversion. The wait-and-see approach consisted of the administration of rate-control medication, including intravenous or oral beta-adrenergic-receptor blocking agents, non-dihydropyridine calcium-channel blockers, or digoxin to achieve a heart rate of 110 beats per minute or less and symptomatic relief. Patients were then discharged with an outpatient visit scheduled for the next day and a referral for cardioversion as close as possible to 48 hours after the onset of symptoms. The cardioconversion group received pharmacologic cardioversion with flecainide unless contraindicated, then electrical cardioversion was performed.

Main outcome measures. Primary outcome was the presence of sinus rhythm on electrocardiogram (ECG) recorded at the 4-week trial visit. Secondary endpoints included the duration of the index visit at the emergency department, emergency department visits related to atrial fibrillation, cardiovascular complications, and time until recurrence of atrial fibrillation.

Main results. From October 2014 through September 2018, 437 patients underwent randomization, with 218 patients assigned to the delayed cardioversion group and 219 to the early cardioversion group. Mean age was 65 years, and a majority of the patients (60%) were men (n = 261). The primary end point of the presence of sinus rhythm on the ECG recorded at the 4-week visit was present in 193 of 212 patients (91%) in the delayed cardioversion group and in 202 of 215 patients (94%) in the early cardioversion group. The –2.9 percentage points with confidence interval [CI] –8.2 to 2.2 (P = 0.005) met the criteria for the noninferiority of the wait-and-see approach.

For secondary outcomes, the median duration of the index visit was 120 minutes (range, 60 to 253) in the delayed cardioversion group and 158 minutes (range, 110 to 228) in the early cardioversion group. The median difference between the 2 groups was 30 minutes (95% CI, 6 to 51 minutes). There was no significant difference in cardiovascular complications between the 2 groups. Fourteen of 212 patients (7%) in the delayed cardioversion group and 14 of 215 patients (7%) in the early cardioversion group had subsequent visits to the emergency department because of a recurrence of atrial fibrillation. Telemetric ECG recordings were available for 335 of the 437 patients. Recurrence of atrial fibrillation occurred in 49 of the 164 (30%) patients in the delayed cardioversion group and 50 of the 171 (29%) patients in the early cardioversion group.

In terms of treatment, conversion to sinus rhythm within 48 hours occurred spontaneously in 150 of 218 patients (69%) in the delayed cardioversion group after receiving rate-control medications only. Of the 218 patients, 61 (28%) had delayed cardioversion (9 by pharmacologic and 52 by electrical cardioversion) as per protocol and achieved sinus rhythm within 48 hours. In the early cardioversion group, conversion to sinus rhythm occurred spontaneously in 36 of 219 patients (16%) before the

initiation of the cardioversion and in 171 of 219 (78%) after cardioversion (83 by pharmacologic and 88 by electrical).

Conclusion. For patients with recent-onset, symptomatic atrial fibrillation, allowing a short time for spontaneous conversion to sinus rhythm is reasonable as demonstrated by this noninferiority study.

Commentary

Atrial fibrillation accounts for nearly 0.5% of all emergency department visits, and this number is increasing.[1,2] Patients commonly undergo immediate restoration of sinus rhythm by means of pharmacologic or electrical cardioversion. However, it is questionable whether immediate restoration of sinus rhythm is necessary, as spontaneous conversion to sinus rhythm occurs frequently. In addition, the safety of cardioversion between 12 and 48 hours after the onset of atrial fibrillation is questionable.[3,4]

In this pragmatic trial, the findings suggest that rate-control therapy alone can achieve prompt symptom relief in almost all eligible patients, had a low risk of complications, and reduced the median length of stay in the emergency department to 2 hours. Independent of cardioversion strategy, the authors stressed the importance of management of stroke risk when patients present with atrial fibrillation to the emergency department. In this trial, 2 patients had cerebral embolism even though both were started on anticoagulation in the index visit. One patient from the delayed cardioversion group was on dabigatran after spontaneous conversion to sinus rhythm and had an event 5 days after the index visit. The other patient, from the early cardioversion group, was on rivaroxaban and had an event 10 days after electrical cardiology. In order for the results of this trial to be broadly applicable, exclusion of intraatrial thrombus on transesophageal echocardiography may be necessary when the onset of atrial fibrillation is not as clear.

There are several limitations of this study. First, this study included only 171 of the 3706 patients (4.6%) screened systematically at the 2 academic centers, but included 266 from 13 centers without systematic screening. The large amount of patients excluded from the controlled environment made the results less generalizable in the broader scope. Second, the reported incidence of recurrent atrial fibrillation within 4 weeks after randomization was an underestimation of the true recurrence rate since the trial used intermittent monitoring. Although the incidence of about 30% was similar between the 2 groups, the authors suggested that the probability of recurrence of atrial fibrillation was not affected by management approach during the acute event. Finally, for these results to be applicable in the general population, defined treatment algorithms and access to prompt follow-up are needed, and these may not be practical in other clinical settings.[2,5]

Applications for Clinical Practice

The current study demonstrated immediate cardioversion is not necessary for patients with recent-onset, symptomatic atrial fibrillation in the emergency department. Allowing a short time for spontaneous conversion to sinus rhythm is reasonable as long as the total time in atrial fibrillation is less than 48 hours. Special consideration for anticoagulation is critical because stroke has been associated with atrial fibrillation duration between 24 and 48 hours.

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